09/134425
Att #14

1. Document ID: US 6180355 B1

L5: Entry 1 of 15

File: USPT

Jan 30, 2001

US-PAT-NO: 6180355
DOCUMENT-IDENTIFIER: US 6180355 B1
TITLE: Method for diagnosing and treating chronic pelvic pain syndrome
DATE-ISSUED: January 30, 2001

US-CL-CURRENT: 435/7.1; 435/7.8

APPL-NO: 9/ 306927
DATE FILED: May 7, 1999

PARENT-CASE:
CROSS-REFERENCE TO RELATED APPLICATION This application claims benefit of U.S. Provisional
Application No. 60/084,668, filed on May 7,1998.

IN: Alexander; Richard B., Ponniah; Sathibalan

AB: The present invention provides a superior method of diagnosing Chronic Pelvic
Pain Syndrome in men comprising measuring levels of cytokines in semen or components or
fractions of semen. The invention also provides a method of treating a condition associated
with elevated levels of a cytokine, such as TNF-.alpha., in semen or a component or fraction
thereof, comprising administering a therapeutically effective amount of an ant-cytokine
compound or composition, such as an anti-TNF-.alpha. compound or composition.

L5: Entry 1 of 15

File: USPT

Jan 30, 2001

DOCUMENT-IDENTIFIER: US 6180355 B1
TITLE: Method for diagnosing and treating chronic pelvic pain syndrome

DETL:
formation of prohormone fragment(s) by proteolysis of the mediated disease prohormone, and uses
of the antibody including prophylactic and therapeutic methods to treat disease, and diagnostic
assays for determining the amount of the prohormone and prohormone fragments present in a
patients body. 5,700,909 Dec 23, Prosaposin and cytokine- Prosaposin and peptide derivatives
derived therefrom will promote neurite outgrowth in 1997 derived peptides vitro. A peptide
consensus sequence was determined by comparing the active neurite outgrowth-inducing saposin C
peptide sequence with that of various hematopoietic and neuropoietic cytokines. These
cytokine-derived peptides will promote the same processes as their corresponding cytokines. In
addition, prosaposin and saposin C promote increased nerve cell myelination ex vivo. 5,700,788
Dec. 23, Ureido derivatives of Subject of the present invention are new ureido derivatives of
naphthalenephosphonic 1997 naphthalenephosphonic acids having the following formula (I) [See
Original Patent for Chemical Structure Diagram] acids (I) [See Original Patent for Chemical
Structure Diagram] wherein each of m and n, which are the same, is an integer of 1 to 4; each of
p and q, which are the same, is an integer of 1 gto 3; and each of the R groups, which are the
same, is a free or esterified phosphonic acid group; and the pharmaceutically acceptable salts
thereof. 5,698,711 Dec. 16, Compounds containing This invention is directed to the pharmaceutical
use of phenyl compounds, which are 1997 phenyl linked to aryl or linked to an aryl moiety by
various linkages, for inhibiting tumor necrosis factor. The heteroaryl by an aliphatic- invention
is also directed to the compounds, their preparation and pharmaceutical or heteroatom-containing
compositions containing these compounds. Furthermore, this invention is directed to the linking
group pharmaceutical use of the compounds for inhibiting cyclic AMP phosphodiesterase. 5,698,706
Dec. 16, Heterocyclic amides and Peptidyl derivatives having a SH or acyl S group and which are
amides, primary amides or 1997 methods of use thioamides, have therapeutic utility via MMP or TNF
inhibition. 5,698,579 Dec. 16, Cyclic amides Cyclic amides are inhibitors of tumor necrosis
factor and can be used to combat cachexia, 1997 endotoxic shock, and retrovirus replication. A
typical embodiment is 3-phenyl-3-(1- oxoisoindolin-2-yl)propionamide. 5,698,564 Dec. 16, Diphenyl
disulfide Diphenyl disulfide compounds having an inhibiting activity against the production of
1997 compounds Interleukin-1 beta (IL-1 beta) or the release of Tumor Necrosis Factor alpha (TNF
alpha), which are useful in the treatment or prophylaxis of the diseases such as chronic
rheumatism and sepsis are described. 5,698,518 Dec. 16, Method for regulating A method of
treating patients to inhibit inflammation is disclosed. In the method, an 1997 inflammation and
tumor effective amount of calmodulin, a calmodulin analogue or calmodulin receptor agonist is
growth with calmodulin, administered to a patient to inhibit production of tumor necrosis factor
and/or augment calmodulin analogues or elastase. In another method, an effective amount of
calmodulin antagonist is administered calmodulin antagonists to a patient to stimulate immune
response or inhibit elastase release. In another embodiment, a diagnostic test is disclosed to be
used on patient blood samples to determine individual propensity to regulate tumor necrosis
factor and/or elastase by calmodulin, its analogues or receptor agonists. 5,698,391 Dec 16,
Methods for synthetic Methods useful for the determination of oligomers which have specific
activity for a target 1997 unrandomization of molecule from a pool of primarily randomly
assembled oligomers are provided. The oligomer fragments disclosed methods involve repeated
syntheses of increasingly simplified sets of oligomers coupled with selection procedures for
determining oligomers having the highest activity. Freedom from the use of enzymes allows the
application of these methods to any molecules which can be oligomerized in a controlled fashion.
5,698,195 Dec. 16, Methods of treating Anti-TNF antibodies, fragments and regions thereof which
are specific for human tumor 1997 rheumatoid arthritis using necrosis factor- alpha (TNF alpha)
and are useful in vivo for diagnosis and therapy of a chimeric anti-TNF number of TNF alpha
-mediated pathologies and conditions, including rheumatoid arthritis antibodies as well as
polynucleotides coding for murine and chimeric antibodies, methods of producing the antibody,
methods of use of the anti-TNF antibody, or fragment, region or derivative thereof, in
immunoassays and immunotherapeutic approaches are provided. 5,695,993 Dec. 9, Cloning and
regulation of Human protein C and activated protein C were shown to bind to endothelium
specifically, 1997 an endothelial cell protein selectively and saturably (Kd = 30 nM, 7000 sites
per cell) in a Ca<2 +> dependent C/activated protein C fashion. Expression

cloning revealed a 1.3
kb CDNA that coded for a novel type receptor transmembrane glycoprotein capable of binding
protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin,
the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR)
function and message are both down regulated by exposure of endothelium to TNF. Identification of
EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in
regulating the inflammatory response, and determination of methods for pharmaceutical use in
manipulating the inflammatory response. 5,695,953 Dec. 9, DNA that encodes a tumor Tumor Necrosis
Factor (TNF) Inhibitory Protein is isolated and substantially purified and 1997 necrosis factor
inhibitory the DNA that encodes the TNF inhibitory protein, vectors, host cells, and a
recombinant protein and a recombinant method for producing the encoded protein are also set
forth. It has the ability to inhibit: (a) method of production the binding of TNF to its
receptors, and (b) the cytotoxic effect of TNF. TNF Inhibitory Protein and salts, functional
derivatives and active fractions thereof can be used to antagonize the deleterious effects of
TNF. 5,691,382 Nov. 25, Inhibition of TNF production The present invention is directed to the
method of inhibiting the release of tumor necrosis 1997 with matrix factor (TNF) in a condition
mediated by TNF by administration of certain hydroxamic add metaloproteinase inhibitors
derivatives, also known as matrix metalloproteinase inhibitors, and thus the method of this
invention is useful in the management of diseases or conditions mediated by TNF. 5,691,381 Nov.
25, Hydroxamic and The present invention provides novel hydroxamic acids and carbocyclic acids
and 1997 carbocyclic acids as derivatives thereof and to pharmaceutical compositions and methods
of use of these novel metalloprotease inhibitors compounds for the inhibition of matrix
metalloproteinases, such as stromelysin, and inhibit the production of tumor necrosis factor
alpha, and for the treatment of arthritis and other related inflammatory diseases. these novel
compounds are represented by Formula I below [See Original Patent for Chemical Structure Diagram]
Formula I 5,688,805 Nov. 18, Tricyclic derivatives, Disclosed are compounds of Formula [See
Original Patent for Chemical Structure 1997 compositions and methods Diagram] (I) or a
pharmaceutically acceptable salt or solvate thereof. Also disclosed are of use pharmaceutical
compositions containing compounds of Formula I, methods for inhibiting tumor necrosis factor-
alpha and methods for treating septic shock, inflammation, or allergic disease. 5,686,455 Nov.
11, Imidazole derivatives and As cytokine inhibitors 2,4,5-triarylimidazole compounds and
compositions for use as 1997 their use as cytokine cytokine inhibitors. inhibitors 5,686,431 Nov.
11, Methods of using low The present invention relates to methods for the prevention and/or
treatment of 1997 molecular weight heparins pathological processes involving the induction of
TNF- alpha secretion comprising a for treatment of pathological pharmaceutically acceptable
carrier and a low molecular Weight heparin (LMWH). In the processes pharmaceutical compositions
of the present invention, the LMWH present in a low effective dose and is administered at
intervals of about 5-8 days. Furthermore, the LMWH is capable of inhibiting in vitro TNF- alpha
secretion by resting T cells and/or macrophages in response to T cell-specific antigens,
mitogens, macrophage activators, disrupted extracellular matrix (dECM), laminin, fibronectin, and
the like. 5,686,259 Nov. 11, Assay method for the Cleavage site blocking antibody that binds to
prohormones, preferable Tumor Necrosis 1997 detection of 26 kd TNF Factor, thereby preventing the
formation of prohormone fragment(s) by proteolysis of the prohormone prohormone, and uses of the
antibody including prophylactic and therapeutic methods to treat disease, and diagnostic assays
for determining the amount of the prohormone and prohormone fragments present in a patients body.
5,684,222 Nov. 4, Mutant mouse having a The multiple biological activities of tumor necrosis
factor (TNF) are mediated by two 1997 disrupted TNFRp55 distinct cell surface receptors of 55 and
75 kDa. Mutant mice of the invention lacking tumor necrosis factor receptor (TNFR) p55 still
express functional TNFRp75 molecules at the cell surface. Normal weight and size of the mutant
mice are not altered. Thymocyle development and lymphocyle populations are normal, and clonal
deletion of potentially self-reactive T cells is not impaired. Activation of the nuclear
transcription factor kappa B (NF- kappa B), however, is completely abrogated after stimulation
with TNF. Moreover, TNFRp55 mutant mice are protected from septic shock induced by bacterial
endotoxin or superantigen, but Listeria clearance is severely impaired and mutant mice easily
succumb to Listeria infection. Thus, the two TNF receptors are not redundant, are independently
controlled, and piay different roles in normal and pathological physiology. 5,679,696 Oct 21,
Compounds containing This invention is directed to the pharmaceutical use of phenyl compounds,
which are 1997 phenyl linked to aryl or linked to an aryl moiety by vanous linkages, for
inhibiting tumor necrosis factor. The heteroaryl by an aliphatic-or invention is also directed to
the compounds, their preparation and pharmaceutical heteroatom-containing compositions containing
these compounds. Furthermore, this invention is directed to the linking group pharmaceutical use
of the compounds for inhibiting cyclic AMP phosphodiesterase. 5,679,684 Oct. 21,
Hydroxyalkylammonium- Novel hydroxyalkylammonium-pyrimidine of the formula [See Original Patent
for Chemical 1997 pyrimidines and nucleoside Structure Diagram] (I) and nucieoside derivatives
have been found to be useful as derivatives, useful as inhibitors of inflammatory cytokines. They
can be used, inter alia, in the therapy of septic inhibitors of inflammatory shock, cachexia,
rheumatoid arthritis, inflammatory bowel disease, multiple sclerosis and cytokines AIDS. The
compounds are typically prepared by reaction of an iodo substituted nucleoside with the
appropriately

2. Document ID: US 6037450 A

L5: Entry 2 of 15

File: USPT

Mar 14, 2000

US-PAT-NO: 6037450
DOCUMENT-IDENTIFIER: US 6037450 A
TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor
DATE-ISSUED: March 14, 2000

US-CL-CURRENT: 530/350; 530/827, 530/830

APPL-NO: 9/ 082021
DATE FILED: May 20, 1998

PARENT-CASE:
This application is a divisional of U.S. Ser. No. 08/884,203, filed Jun. 27, 1997.

IN: Esmon; Charles T., Stearns-Kurosawa; Deborah J., Kurosawa; Shinichiro

AB: Plasma EPCR has been isolated, characterized and shown to block cellular protein
C activation and APC anticoagulant activity. Plasma EPCR appears to be about 43,000 daltons
and circulates at approximately 100 ng/ml (98.4.+-.27.8 ng/ml, n=22). Plasma EPCR bound
activated protein C with an affinity similar to that of recombinant soluble EPCR (Kd.sub.app
approximately 30 nM), and inhibits both protein C activation on an endothelial cell line and
APC anticoagulant activity in a one-stage factor Xa clotting assay. Soluble plasma EPCR
appears to attenuate the membrane-bound EPCR augmentation of protein C activation and the
anticoagulant function of activated protein C. Soluble EPCR has also been detected in urine.
Levels of soluble EPCR can rise in inflammatory disease associated with vascular injury and
appear to be correlated with inflammation and disease states associated with abnormal
coagulation. Since EPCR expression is restricted to larger vessels and is usually negative
in cappillaries, these observations provide a mechanism for analyzing injury/stimulation of
large vessel endothelial cells.

L5: Entry 2 of 15

File: USPT

Mar 14, 2000

DOCUMENT-IDENTIFIER: US 6037450 A
TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

BSPR:
The present invention is generally in the area of assays involving detection and/or measurement
of endothelial cell protein C/activated protein C receptor or soluble forms thereof derived
either by proteolysis or by alternative splicing.

BSPR:
EPCR is a recently identified receptor with significant homology to the CD1/MHC class I family
(Fukudome and Esmon, 1994; Fukudome, et al. 1996. J. Biol. Chem. 271:17491-17498; Regan, et al.
1996. J. Biol. Chem. 271:17499-17503). The cloning and biological role of the endothelial cell
receptor for protein C was described in PCT/US95/09636 by Oklahoma Medical Research Foundation,
entitled "Cloning and Regulation of an Endothelial Cell Protein C/Activated Protein C Receptor".
The protein was predicted to consist of 238 amino acids, which includes a 15 amino acid signal
sequence at the N-terminus, and a 23 amino acid transmembrane region which characterizes the
receptor as a type I transmembrane protein.

DEPR:
Endothelial Protein C Receptor, EPCR.

DEPC:
Identification of Functional Endothelial Protein C Receptor in Human Plasma

CLPR:
1. A modified endothelial protein C receptor having the structure of the protein defined by Seq.
ID No. 2, residues 16-238 wherein the carboxyl terminal cysteine residue is replaced with another
amino acid or is not palmitoylated.

CLPR:
2. The modified endothelial protein C receptor of claim 1 which is not glycosylated.

CLPR:
3. The modified endothelial protein C receptor of claim 1 further comprising a signal sequence
having the structure of Seq. ID No. 2, residues 1-15.

CLPR:
4. The modified endothelial protein C receptor of claim 1 encoded by Seq. ID No. 1, or a
nucleotide sequence hybridizing thereto under stringent conditions.

CLPR:
5. The modified endothelial protein C receptor of claim 4 encoded by Seq. ID No. 1.

CLPR:
6. The modified endothelial protein C receptor of claim 1 wherein the carboxyl terminal cysteine
residue is replaced with another amino acid.

CLPR:
7. The modified endothelial protein C receptor of claim 1 wherein the carboxyl terminal cysteine
residue is not palmitoylated.

CLPR:
8. The modified endothelial protein C receptor of claim 1 which is human endothelial protein C
receptor except for the modification.

CLPR:
9. An isolated naturally occurring alternatively spliced endothelial protein C receptor present
in plasma having the structure defined by Seq. ID No. 2, further comprising a protein insert
after Gly 201.

CLPR:
10. The isolated naturally occurring alternatively spliced endothelial protein C receptor of
claim 9 comprising protein inserts as shown in FIG. 3.

CLPR:
11. An isolated naturally occurring soluble endothelial protein C receptor having the structure
of Seq. ID No. 2, residues 16-201, wherein the receptor has been cleaved at a naturally occuring
proteolytic cleavage site before the transmembrane domain present in plasma.

CLPR:
12. The isolated naturally occurring soluble endothelial protein C receptor of claim 11 encoded
by a DNA sequence hybridizing to Seq. ID No. 1 under stringent conditions.

ORPL:
Kurosawa, et al., "Identification of functional Endothelial Protein C Receptor in Human Plasma,"
J. Clin. Invest. 1000(2): 411-418 (1997).

ORPL:
Fukudome and Esmon, "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell
Protein C/Activated Protein C Receptor (EPCR)--The Structural and

Functional Conservation in
Human, Bovine and Murine EPCR*," J. Biol. Chem. 270(10):5571-5577 (1995).

ORPL:
Laszik, et al., "The Human Protein C Receptor Is Present Primarily on Endothelium of Large Blood
Vessels," Circulation, 96(10):1-9 (1997).

ORPL:
Regan, et al., "The Endothelial Cell Protein C Receptor--Inhibition of Activated Protein C
Anticoagulant Function without Modulation of Reaction with Proteinase Inhibitors*," J. Biol.
Chem. 271(29):17499-17503 (1996).

ORPL:
Steams-Kurosawa, et al., "The endothelial cell protein C receptor augments protein C activation
by the thrombin-thrombomodulin complex," Proc. Nation Acad. Sci. (USA) 93:10212-10216 (1996).

3. Document ID: US 5852171 A

L5: Entry 3 of 15

File: USPT

Dec 22, 1998

US-PAT-NO: 5852171
DOCUMENT-IDENTIFIER: US 5852171 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor
DATE-ISSUED: December 22, 1998

US-CL-CURRENT: 530/350; 530/380

APPL-NO: 8/ 878283
DATE FILED: June 18, 1997

PARENT-CASE:
This is a divisional of U.S. Ser. No. 08/289,699, filed on Aug. 12, 1994, now U.S. Pat. No.
5,695,993.

IN: Fukudome; Kenji, Esmon; Charles T.

AB: Human protein C and activated protein C were shown to bind to endothelium
specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+
dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I
transmembrane glycoprotein capable of binding protein C. This protein appears to be a member
of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C
activation, the endothelial cell protein C receptor (EPCR) function and message are both
down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the
CD1/MHC superfamily provides insights into the role of protein C in regulating the
inflammatory response, and determination of methods for pharmaceutical use in manipulating
the inflammatory response.

L5: Entry 3 of 15

File: USPT

Dec 22, 1998

DOCUMENT-IDENTIFIER: US 5852171 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

ABPL:
Human protein C and activated protein C were shown to bind to endothelium specifically,
selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+ dependent fashion.
Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane
glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC
superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial
cell protein C receptor (EPCR) function and message are both down regulated by exposure of
endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides
insights into the role of protein C in regulating the inflammatory response, and determination of
methods for pharmaceutical use in manipulating the inflammatory response.

BSPR:
The present invention is generally in the area of cloning, expression, and regulation of an
endothelial cell protein C/activated protein C receptor.

DEPR:
Expression cloning revealed a 1.3 kb cDNA that coded for a type I transmembrane glycoprotein
capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily.
Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein
C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF.
Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of
this receptor for protein C in regulating the inflammatory response.

DEPR:
The identification of the protein C receptor on endothelium suggests that the endothelial cell
binds protein C/APC through three distinct mechanisms. In addition to EPCR, protein S can bind
APC/protein C on negatively charged membrane surfaces that include the endothelium (Stern et al.,
(1986) J. Biol. Chem. 261, 713-718), but this is not cell type specific (Dahlback et al., 1992).
Thrombomodulin in complex with thrombin can bind protein C and APC (Hogg et al., 1992). On
endothelium, the protein S binding sites (Nawroth and Stern, (1986) J. Exp. Med. 163, 740-745),
thrombomodulin (Esmon, 1989) and EPCR are all down regulated by cytokines, indicating that
inflammation can impair protein C pathway function at multiple levels.

DEPR:
As described herein, a variety of compounds can be used to inhibit or enhance expression of the
EPCR. The nature of the disorder will determine if the expression should be enhanced or
inhibited. For example, based on the studies involving the use of an anti-protein C antibody in
combination with cytokine, it should be possible to treat solid tumors by enhancing an
inflammatory response involving blocking of protein C or activated protein C binding to an
endothelial cell protein C/activated protein C receptor by administering to a patient in need of
treatment thereof an amount of a compound blocking binding of protein C or activated protein C to
the receptor. Similarly, it should be possible to treat disorders such as gram negative sepsis,
stroke, thrombosis, septic shock, adult respiratory distress syndrome, and

pulmonary emboli using
a method for inhibiting an inflammatory response involving administration of EPCR or EPCR
fragments or substances that upregulate EPCR expression to a patient in need of treatment therof.

CLPR:
1. An isolated endothelial cell protein C/activated protein C receptor having the amino acid
sequence of Sequence ID No. 2 or a sequence having conservative substitutions, additions or
deletions thereof, having functionally equivalent receptor binding activity to activated Protein
C.

4. Document ID: US 5804392 A

L5: Entry 4 of 15
File: USPT
Sep 8, 1998

US-PAT-NO: 5804392
DOCUMENT-IDENTIFIER: US 5804392 A
TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor
DATE-ISSUED: September 8, 1998

US-CL-CURRENT: 435/7.1; 435/7.8, 435/975, 436/506, 530/387.1, 530/388.22, 530/389.1

APPL-NO: 8/ 884203
DATE FILED: June 27, 1997

IN: Esmon; Charles T., Stearns-Kurosawa; Deborah J., Kurosawa; Shinichiro

AB: Plasma EPCR has been isolated, characterized and shown to block cellular protein
C activation and APC anticoagulant activity. Plasma EPCR appears to be about 43,000 daltons
and circulates at approximately 100 ng/ml (98.4.+-.27.8 ng/ml, n=22). Plasma EPCR bound
activated protein C with an affinity similar to that of recombinant soluble EPCR (Kd.sub.app
approximately 30 nM), and inhibits both protein C activation on an endothelial cell line and
APC anticoagulant activity in a one-stage factor Xa clotting assay. Soluble plasma EPCR
appears to attenuate the membrane-bound EPCR augmentation of protein C activation and the
anticoagulant function of activated protein C. Soluble EPCR has also been detected in urine.
Levels of soluble EPCR can rise in inflammatory disease associated with vascular injury and
appear to be correlated with inflammation and disease states associated with abnormal
coagulation. Since EPCR expression is restricted to larger vessels and is usually negative
in cappillaries, these observations provide a mechanism for analyzing injury/stimulation of
large vessel endothelial cells.

L5: Entry 4 of 15
File: USPT
Sep 8, 1998

DOCUMENT-IDENTIFIER: US 5804392 A

TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

BSPR:
The present invention is generally in the area of assays involving detection and/or measurement
of endothelial cell protein C/activated protein C receptor or soluble forms thereof derived
either by proteolysis or by alternative splicing.

BSPR:
EPCR is a recently identified receptor with significant homology to the CD1/MHC class 1 family
(Fukudome and Esmon, 1994; Fukudome, et al. 1996. J. Biol. Chem. 271:17491-17498; Regan, et al.
1996. J. Biol. Chem. 271:17499-17503). The cloning and biological role of the endothelial cell
receptor for protein C was described in PCT/US95/09636 by Oklahoma Medical Research Foundation,
entitled "Cloning and Regulation of an Endothelial Cell Protein C/Activated Protein C Receptor".
The protein was predicted to consist of 238 amino acids, which includes a 15 amino acid signal
sequence at the N-terminus, and a 23 amino acid transmembrane region which characterizes the
receptor as a type 1 transmembrane protein.

DEPR:
Endothelial Protein C Receptor, EPCR.

DEPC:
Identification of Functional Endothelial Protein C Receptor in Human Plasma

CLPR:
1. An assay for soluble endothelial protein C receptor comprising

CLPR:
3. The assay of claim 1 further comprising the step of correlating the amount of soluble
endothelial protein C receptor with calibration standards.

CLPR:
8. A kit for detection and measurement of endothelial protein C receptor comprising

CLPR:
9. The kit of claim 8 where the antibody has a higher affinity for endothelial protein C receptor
including the transmembrane domain than for endothelial protein C receptor not including the
transmembrane domain.

CLPR:
10. The kit of claim 8 wherein the antibody is immunoreactive with the insert in an alternatively
spliced endothelial protein C receptor.

CLPR:
11. The kit of claim 8 wherein the antibodies block binding of endothelial protein C receptor and
activated protein C or protein C.

CLPV:
measuring the amount of soluble endothelial protein C receptor.

CLPV:
an antibody immunoreactive with endothelial protein C receptor,

CLPV:
reagents to detect a reaction between the antibody and endothelial protein C receptor in a sample
from a patient, and

CLPV:
standards to correlate the amount of reaction to normal and abnormal levels of endothelial

protein C receptor.

ORPL:
Fukudome, et al., "The Endothelial Cell Protein C Receptor--Cell Surface Expression and Direct
Ligand Binding by the Soluble Receptor," J. Biol. Chem. 271(29):17491-17498 (1996).

ORPL:
Fukudome and Esmon, "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell
Protein C/Activated Protein C Receptor (EPCR)--The Structural and Functional Conservation in
Human, Bovine and Murine EPCR*," J. Biol. Chem. 270(10):5571-5577 (1995).

ORPL:
Regan, et al., "The Endothelial Cell Protein C Receptor--Inhibition of Activated Protein C
Anticoagulant Function without Modulation of Reaction with Proteinase Inhibitors*," J. Biol.
Chem. 271(29):17499-17503 (1996).

5. Document ID: US 5695993 A

L5: Entry 5 of 15

File: USPT

Dec 9, 1997

US-PAT-NO: 5695993
DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor
DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 435/325; 435/320.1, 435/69.1, 536/23.5

APPL-NO: 8/ 289699
DATE FILED: August 12, 1994

IN: Fukudome; Kenji, Esmon; Charles T.

AB: Human protein C and activated protein C were shown to bind to endothelium
specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+
dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I
transmembrane glycoprotein capable of binding protein C. This protein appears to be a member
of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C
activation, the endothelial cell protein C receptor (EPCR) function and message are both
down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the
CD1/MHC superfamily provides insights into the role of protein C in regulating the
inflammatory response, and determination of methods for pharmaceutical use in manipulating
the inflammatory response.

L5: Entry 5 of 15

File: USPT

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

ABPL:
Human protein C and activated protein C were shown to bind to endothelium specifically,
selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+ dependent fashion.
Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane
glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC
superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial
cell protein C receptor (EPCR) function and message are both down regulated by exposure of
endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides
insights into the role of protein C in regulating the inflammatory response, and determination of
methods for pharmaceutical use in manipulating the inflammatory response.

BSPR:
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DEPR:
Expression cloning revealed a 1.3 kb cDNA that coded for a type I transmembrane glycoprotein
capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily.
Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein
C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF.
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this receptor for protein C in regulating the inflammatory response.

DEPR:
The identification of the protein C receptor on endothelium suggests that the endothelial cell
binds protein C/APC through three distinct mechanisms. In addition to EPCR, protein S can bind
APC/protein C on negatively charged membrane surfaces that include the endothelium (Stern et al.,
(1986) J. Biol. Chem. 261, 713-718), but this is not cell type specific (Dahlback et al., 1992).
Thrombomodulin in complex with thrombin can bind protein C and APC (Hogg et al., 1992). On
endothelium, the protein S binding sites (Nawroth and Stern, (1986) J. Exp. Med. 163, 740-745),
thrombomodulin (Esmon, 1989) and EPCR are all down regulated by cytokines, indicating that
inflammation can impair protein C pathway function at multiple levels.

DEPR:
As described herein, a variety of compounds can be used to inhibit or enhance expression of the
EPCR. The nature of the disorder will determine if the expression should be enhanced or
inhibited. For example, based on the studies involving the use of an anti-protein C antibody in
combination with cytokine, it should be possible to treat solid tumors by enhancing an
inflammatory response involving blocking of protein C or activated protein C binding to an
endothelial cell protein C/activated protein C receptor by administering to a patient in need of
treatment thereof an amount of a compound blocking binding of protein C or activated protein C to
the receptor. Similarly, it should be possible to treat disorders such as gram negative sepsis,
stroke, thrombosis, septic shock, adult respiratory distress syndrome, and pulmonary emboli using
a method for inhibiting an inflammatory response involving administration of EPCR or EPCR

fragments or substances that upregulate EPCR expression to a patient in need of treatment therof.

CLPR:
6. An isolated nucleic acid molecule as set forth in SEQ ID No. 1 encoding an endothelial cell
protein C/activated protein C receptor protein.

ORPL:
Fukudome, K. et al., "Molecular Cloning and Expression of Murine and Bovine Endothelial Cell
Protein C/activated Protein C Receptor (EPCR)", J. Biological Chemistry, vol. 270, no. 10, pp.
5571-5577 (1995).

ORPL:
Fukudome, K. et al., "Identification, Cloning, and Regulation of Novel Endothelial Cell Protein
C/activated Protein C Receptor", Circulation, vol. 90, no. 4, pt. 2, pp. I-N, 1133 (1994).

ORPL:
Fukudome, K. et al., "Identification, Cloning, and Regulation of Novel Endothelial Cell Protein
C/activated Protein C Receptor", J. Biological Chemistry, vol. 269, No. 42, pp. 26486-26491
(1994).

6. Document ID: US 5665556 A

L5: Entry 6 of 15

File: USPT

Sep 9, 1997

US-PAT-NO: 5665556
DOCUMENT-IDENTIFIER: US 5665556 A
TITLE: Complement components and binding ligands in fertility
DATE-ISSUED: September 9, 1997

US-CL-CURRENT: 435/7.21; 435/2, 435/7.2, 435/806, 436/510, 436/518, 436/519, 436/65, 436/821,
436/906, 530/852

APPL-NO: 8/ 441067
DATE FILED: May 15, 1995

PARENT-CASE:
This application is a continuation application of U.S. application Ser. No. 08/137,820, filed
Oct. 19, 1993, now U.S. Pat. No. 5,474,927, which is a continuation application of U.S.
application Ser. No. 07/487,039, filed Mar. 2, 1990, now abandoned.

IN: Anderson; Deborah J., Johnson; Peter M., Jack; Richard M.

AB: Methods for detecting and isolating acrosome-reacted sperm and complement
receptor-bearing oocytes using the complement component C3, fragments, or variants thereof,
antibodies to a complement receptor, or antibodies to C3, are disclosed. These methods have
application in the assessment of fertility, in the preparation of sperm or oocytes for in
vitro fertilization or for gamete intrafallopian tube transfer, in promoting or inhibiting
fertilization in vitro and in vivo, and in diagnosing and treating infertility.

L5: Entry 6 of 15

File: USPT

Sep 9, 1997

DOCUMENT-IDENTIFIER: US 5665556 A
TITLE: Complement components and binding ligands in fertility

DEPR:
This invention is based on the recognition by the inventors that acrosome-reacted sperm bound to
a mAb (H316) directed to a trophoblast cell surface antigen, and that the same antigen, present
on leucocytes as well, was identical to a C binding protein, gp45-70, also known as the membrane
cofactor protein (MCP). The antigen identified by the H316 mAb which is identical to MCP is also
the same as the HuLy-m5 antigen (Johnson, P. M. et al., in: Reproductive Immunology 1989, Mettler
& Billington (eds.), Elsevier, Amsterdam (in press). Under the current system of nomenclature,
this antigen has been designated CD46. As a result of this discovery, the inventors conceived of
a role for MCP, as a C binding protein or a C receptor (CR) on the surface of gametes, in the
process of sperm-egg interaction during the fertilization process. The invention is therefore
directed to the exploitation of the presence of this CR on gametes in the diagnosis of
infertility, in the identification and isolation of acrosome-reacted sperm, in the promotion or
inhibition of fertilization in vitro or in vivo, and in the treatment of infertility.

7. Document ID: US 5474927 A

L5: Entry 7 of 15

File: USPT

Dec 12, 1995

US-PAT-NO: 5474927
DOCUMENT-IDENTIFIER: US 5474927 A
TITLE: Complement components and binding ligands in fertility
DATE-ISSUED: December 12, 1995

US-CL-CURRENT: 435/7.21; 435/806, 436/510, 436/519, 436/65, 436/821, 436/906

APPL-NO: 8/ 137820
DATE FILED: October 19, 1993

PARENT-CASE:
This application is a continuation of application Ser. No. 07/487,039, filed Mar. 2, 1990,
abandoned.

IN: Anderson; Deborah J., Johnson; Peter M., Jack; Richard M.

AB: Methods for detecting and isolating acrosome-reacted sperm and complement
receptor-bearing oocytes using the complement component C3, fragments, or variants thereof,
antibodies to a complement receptor, or antibodies to C3, are disclosed. These methods have
application in the assessment of fertility, in the preparation of sperm or oocytes for in
vitro fertilization or for gamete intrafallopian tube transfer, in promoting or inhibiting
fertilization in vitro and in vivo, and in diagnosing and treating infertility.

L5: Entry 7 of 15

File: USPT

Dec 12, 1995

DOCUMENT-IDENTIFIER: US 5474927 A
TITLE: Complement components and binding ligands in fertility

DEPR:
This invention is based on the recognition by the inventors that acrosome-reacted sperm bound to a mAb (H316) directed to a trophoblast cell surface antigen, and that the same antigen, present on leucocytes as well, was identical to a C binding protein, gp45-70, also known as the membrane cofactor protein (MCP). The antigen identified by the H316 mAb which is identical to MCP is also the same as the HuLy-m5 antigen (Johnson, P. M. et al., in: Reproductive Immunology 1989, Mettler & Billington (eds.), Elsevier, Amsterdam (in press). Under the current system of nomenclature, this antigen has been designated CD46. As a result of this discovery, the inventors conceived of a role for MCP, as a C binding protein or a C receptor (CR) on the surface of gametes, in the process of sperm-egg interaction during the fertilization process. The invention is therefore directed to the exploitation of the presence of this CR on gametes in the diagnosis of infertility, in the identification and isolation of acrosome-reacted sperm, in the promotion or inhibition of fertilization in vitro or in vivo, and in the treatment of infertility.

8. Document ID: US 5804392 A

L5: Entry 8 of 15

File: EPAB

Sep 8, 1998

PUB-NO: US005804392A
DOCUMENT-IDENTIFIER: US 5804392 A
TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

PUBN-DATE: September 8, 1998

INT-CL (IPC): G01N 33/53; G01N 33/564; C07K 16/28

APPL-NO: US88420397
APPL-DATE: June 27, 1997

PRIORITY-DATA:

IN: ESMON, CHARLES T, STEARNS-KUROSAWA, DEBORAH J, KUROSAWA, SHINICHIRO

AB: Plasma EPCR has been isolated, characterized and shown to block cellular protein C activation and APC anticoagulant activity. Plasma EPCR appears to be about 43,000 daltons and circulates at approximately 100 ng/ml (98.4+/-27.8 ng/ml, n=22). Plasma EPCR bound activated protein C with an affinity similar to that of recombinant soluble EPCR (Kdapp approximately 30 nM), and inhibits both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage factor Xa clotting assay. Soluble plasma EPCR appears to attenuate the membrane-bound EPCR augmentation of protein C activation and the anticoagulant function of activated protein C. Soluble EPCR has also been detected in urine. Levels of soluble EPCR can rise in inflammatory disease associated with vascular injury and appear to be correlated with inflammation and disease states associated with abnormal coagulation. Since EPCR expression is restricted to larger vessels and is usually negative in cappillaries, these observations provide a mechanism for analyzing injury/stimulation of large vessel endothelial cells.

L5: Entry 8 of 15

File: EPAB

Sep 8, 1998

DOCUMENT-IDENTIFIER: US 5804392 A
TITLE: Diagnostic assays using soluble endothelial cell protein C/activated protein C receptor

9. Document ID: US 5695993 A

L5: Entry 9 of 15

File: EPAB

Dec 9, 1997

PUB-NO: US005695993A
DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

PUBN-DATE: December 9, 1997

INT-CL (IPC): C12N 5/16; C07H 21/04
EUR-CL (EPC): C07K014/705

APPL-NO: US28969994
APPL-DATE: August 12, 1994

PRIORITY-DATA:

IN: FUKUDOME, KENJI, ESMON, CHARLES T

AB: Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca2+ dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

L5: Entry 9 of 15

File: EPAB

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

FPAR:
Human protein C and activated protein C were shown to bind to endothelium specifically,
selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca2+ dependent fashion. Expression
cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable
of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like
thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C
receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF.
Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of
protein C in regulating the inflammatory response, and determination of methods for
pharmaceutical use in manipulating the inflammatory response.

10. Document ID: WO 9605303 A1

L5: Entry 10 of 15

File: EPAB

Feb 22, 1996

PUB-NO: WO009605303A1
DOCUMENT-IDENTIFIER: WO 9605303 A1
TITLE: CLONING AND REGULATION OF AN ENDOTHELIAL CELL PROTEIN C/ACTIVATED PROTEIN C RECEPTOR

PUBN-DATE: February 22, 1996

INT-CL (IPC): C12N 15/12; C07K 14/705; A61K 39/395; C12N 15/11; A61K 38/17; C07K 16/28; G01N 33/68
EUR-CL (EPC): C07K014/705

APPL-NO: US09509636
APPL-DATE: August 9, 1995

PRIORITY-DATA:

IN: FUKUDOME, KENJI, ESMON, CHARLES T

AB: Human protein C and activated protein C were shown to bind to endothelium
specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca<2+>
dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I
transmembrane glycoprotein capable of binding protein C. This protein appears to be a member
of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C
activation, the endothelial cell protein C receptor (EPCR) function and message are both
down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the
CD1/MHC superfamily provides insights into the role of protein C in regulating the
inflammatory response, and determination of methods for pharmaceutical use in manipulating
the inflammatory response.

L5: Entry 10 of 15

File: EPAB

Feb 22, 1996

DOCUMENT-IDENTIFIER: WO 9605303 A1
TITLE: CLONING AND REGULATION OF AN ENDOTHELIAL CELL PROTEIN C/ACTIVATED PROTEIN C RECEPTOR

FPAR:
Human protein C and activated protein C were shown to bind to endothelium specifically,
selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca<2+> dependent fashion.
Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane
glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC
superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial
cell protein C receptor (EPCR) function and message are both down regulated by exposure of
endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides
insights into the role of protein C in regulating the inflammatory response, and determination of
methods for pharmaceutical use in manipulating the inflammatory response.

11. Document ID: US 6037450 A

L5: Entry 11 of 15

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-246200
DERWENT-WEEK: 200023

TITLE: Modified endothelial protein C receptor, useful as diagnostic marker of e.g. inflammation
or autoimmune diseases, is a soluble or alternatively spliced form of the receptor

PRIORITY-DATA: 1997US-0884203 (June 27, 1997), 1998US-0082021 (May 20, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6037450 A	March 14, 2000	N/A	024	C07K014/705

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 6037450A			

June 27, 1997
1997US-0884203
Div ex
US 6037450A
May 20, 1998
1998US-0082021
N/A

INT-CL (IPC): C07K 14/705

IN: ESMON, C T, KUROSAWA, S, STEARNS-KUROSAWA, D J

AB: NOVELTY - Modified endothelial protein C receptor (I) comprises amino acids (aa)
16-238 of a 238 aa sequence (S2) given in the specification, and has the C-terminal Cys
replaced by some other aa, or is not palmitoylated., DETAILED DESCRIPTION - INDEPENDENT
CLAIMS are also included for the following:, (1) isolated, natural alternatively spliced
form (Ia) of (I), comprising (S2) with a protein insertion after Gly 201; and, (2) isolated,
natural form (Ib) of (I) comprising residues 16-201 of (S2) that has been cleaved, in
plasma, at a protease site before the transmembrane domain., ACTIVITY - None given.,
MECHANISM OF ACTION - (I) blocks activation of cellular protein C and anticoagulant activity
of activated protein C., USE - (I) blocks activation of cellular protein C and anticoagulant
activity of activated protein C. Measurement of (I), in standard immunoassays, is used to
diagnose disorders involving coagulation or inflammation, or autoimmune diseases (e.g. lupus
erythematosus; sepsis; diabetes; pre-eclampsia; restenosis and many others) also for
monitoring treatment. (I) is a marker of endothelial cells so its presence may also indicate
damage to large blood vessels, e.g. drug-induced damage. The antibodies used for immunoassay
may also be used to characterize and isolate receptor proteins and to modulate receptor
protein activity, particularly to inhibit binding to ligands.

L5: Entry 11 of 15
File: DWPI
Mar 14, 2000

DERWENT-ACC-NO: 2000-246200
DERWENT-WEEK: 200023
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TITLE: Modified endothelial protein C receptor, useful as diagnostic marker of e.g. inflammation
or autoimmune diseases, is a soluble or alternatively spliced form of the receptor

ABTX:
NOVELTY - Modified endothelial protein C receptor (I) comprises amino acids (aa) 16-238 of a 238
aa sequence (S2) given in the specification, and has the C-terminal Cys replaced by some other
aa, or is not palmitoylated.

12. Document ID: AU 9959013 A, WO 200010609 A1
L5: Entry 12 of 15
File: DWPI
Mar 14, 2000

DERWENT-ACC-NO: 2000-224557
DERWENT-WEEK: 200031
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful for treatment or
diagnosis of cardiovascular disease, by targeting the endothelial cell protein-C receptor

PRIORITY-DATA: 1998US-0139425 (August 25, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 9959013 A	March 14, 2000	N/A	000	A61K045/06
WO 200010609 A1	March 2, 2000	E	023	A61K045/06

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 9959013A	August 25, 1999	1999AU-0059013	N/A
AU 9959013A		WO 200010609	Based on
WO 200010609A1	August 25, 1999	1999WO-US19480	N/A

INT-CL (IPC): A61K 45/06

IN: ESMON, C T, XU, J

AB: NOVELTY - A method of selectively delivering molecules (I) to the nucleus of
endothelial cells of large vessels by administering a conjugate (C) of (I) with an agent
(II) that binds selectively to endothelial protein C receptor (EPCR)., DETAILED DESCRIPTION
- An INDEPENDENT CLAIM is also included for a conjugate of (I) which is not a diagnostic
label, with either protein C, optionally activated, or an antibody reactive with EPCR, or
fragments of it which bind EPCR., ACTIVITY - Antithrombotic; fibrinolytic; antiinflammatory;
anticoagulant; vasoconstrictor., MECHANISM OF ACTION - EPCR translocates from the plasma
membrane to the nucleus, and transports molecules that bind to it., USE - (C) are used to
deliver therapeutic agents, e.g. nucleic acids, proteins, expression inhibitors,
anti-inflammatories, anticoagulants, growth hormones etc., or diagnostic agents such as
radiolabels, fluorescent labels and enzymatic labels, particularly in the cases of
cardiovascular disease. Typical applications include preventing thrombosis, increasing
fibrinolytic activity, or inhibiting leukocyte adhesion., ADVANTAGE - Since EPCR is present
mainly on endothelial cells of large vessels, rather than similar cells in

capillaries or
other small vessels, especially in arteries, using it as target provides selective delivery
of (I) with reduced risks of systemic complications. Serum stimulates nuclear translocation
of EPCR, so delivery is enhanced during inflammatory or coagulative processes, often present
in the treated subjects.

L5: Entry 12 of 15
File: DWPI
Mar 14, 2000

DERWENT-ACC-NO: 2000-224557
DERWENT-WEEK: 200031
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TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful for treatment or
diagnosis of cardiovascular disease, by targeting the endothelial cell protein C receptor

ABTX:
NOVELTY - A method of selectively delivering molecules (I) to the nucleus of endothelial cells of
large vessels by administering a conjugate (C) of (I) with an agent (II) that binds selectively
to endothelial protein C receptor (EPCR).

13. Document ID: US 5804392 A, WO 9900673 A1, AU 9882694 A, EP 991946 A1
L5: Entry 13 of 15
File: DWPI
Sep 8, 1998

DERWENT-ACC-NO: 1998-505645
DERWENT-WEEK: 200023
COPYRIGHT 2001 DERWENT INFORMATION LTD

TITLE: Immuno-based detection of protein C receptor - useful in the diagnosis of inflammatory and
coagulation states and disorders associated with damage to endothelium and large blood vessel
disease

PRIORITY-DATA: 1997US-0884203 (June 27, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5804392 A	September 8, 1998	N/A	023	G01N033/53
WO 9900673 A1	January 7, 1999	E	000	G01N033/68
AU 9882694 A	January 19, 1999	N/A	000	G01N033/68
EP 991946 A1	April 12, 2000	E	000	G01N033/68

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 5804392A	June 27, 1997	1997US-0884203	N/A
WO 9900673A1	June 26, 1998	1998WO-US13385	N/A
AU 9882694A	June 26, 1998	1998AU-0082694	N/A
AU 9882694A		WO 9900673	Based on
EP 991946A1	June 26, 1998	1998EP-0932912	N/A
EP 991946A1	June 26, 1998	1998WO-US13385	N/A
EP 991946A1		WO 9900673	Based on

INT-CL (IPC): C07K 14/705; C07K 16/28; G01N 33/53; G01N 33/564; G01N 33/68

IN: ESMON, C T, KUROSAWA, S, STEARNS-KUROSAWA, D J

AB: An assay for soluble endothelial protein C receptor comprises containing a,
sample from a patient to be tested and measuring the amount of soluble endothelial protein C
receptor., Also claimed is a kit for detection and measurement of endothelial protein C
receptor comprising:, (a) an antibody immunoreactive with endothelial protein C receptor:,
(b) reagents to detect a reaction between the Ab and endothelial protein C receptor in a
patient sample; and, (c) standards to correlate the amount of reaction to normal and
abnormal levels of endothelial protein C receptor., USE - The assay is used for the
diagnosis of coagulation and inflammatory states and disorders, damage to endothelium, and
large blood vessel disease, e.g. autoimmune diseases, transplantation, sepsis, shock,
pre-eclampsia, diabetes, vascular disease (especially cardiopulmonary bypass, unstable
angina, restenosis and angioplasty), kidney disease and liver disease (claimed). Protein C
is involved in the regulation of a host response to inflammation. The protein is one of the
last components to be activated in the coagulation system, and is thought to control
coagulation and inflammation. Activation of the receptor through a pathway involving
thrombin, activates protein C. The protein C pathway is apparently only involved in large
blood vessels, not capillaries, and so is activated with for major vascular conditions, and
the increased presence of the receptor in the conditions stated makes it ideal as a

diagnostic component.

L5: Entry 13 of 15
File: DWPI
Sep 8, 1998

DERWENT-ACC-NO: 1998-505645
DERWENT-WEEK: 200023

TITLE: Immuno-based detection of protein C receptor - useful in the diagnosis of inflammatory and
coagulation states and disorders associated with damage to endothelium and large blood vessel
disease

ABTX :
An assay for soluble endothelial protein C receptor comprises containing a

ABTX:
sample from a patient to be tested and measuring the amount of soluble endothelial protein C
receptor.

ABTX:
Also claimed is a kit for detection and measurement of endothelial protein C receptor comprising:

ABTX:
(a) an antibody immunoreactive with endothelial protein C receptor;

ABTX:
(b) reagents to detect a reaction between the Ab and endothelial protein C receptor in a patient
sample; and

ABTX:
(c) standards to correlate the amount of reaction to normal and abnormal levels of endothelial
protein C receptor.

14. Document ID: AU 719629 B, WO 9820041 A1, AU 9854317 A, EP 937104 A1
L5: Entry 14 of 15
File: DWPI
May 11, 2000

DERWENT-ACC-NO: 1998-286871
DERWENT-WEEK: 200031

TITLE: Regulatory elements from the endothelial protein C receptor promoter - useful to direct
expression of genes or nucleotide molecules e.g. to endothelial cells or only large vessel
endothelial cells in gene therapy

PRIORITY-DATA: 1997US-0054533 (August 4, 1997), 1996US-0030718 (November 8, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 719629 B	May 11, 2000	N/A	000	C07K014/705
WO 9820041 A1	May 14, 1998	E	069	C07K014/705
AU 9854317 A	May 29, 1998	N/A	000	C07K014/705
EP 937104 A1	August 25, 1999	E	000	C07K014/705

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 719629B	November 7, 1997	1998AU-0054317	N/A
AU 719629B		AU 9854317	Previous Publ.
AU 719629B		WO 9820041	Based on
WO 9820041A1	November 7, 1997	1997WO-US20364	N/A
AU 9854317A	November 7, 1997	1998AU-0054317	N/A
AU 9854317A		WO 9820041	Based on
EP 937104A1	November 7, 1997	1997EP-0948205	N/A
EP 937104A1	November 7, 1997	1997WO-US20364	N/A
EP 937104A1		WO 9820041	Based on

INT-CL (IPC): C07H 21/04; C07K 14/705; C12N 15/12

IN: ESMON, C T, GU, J

AB: Regulatory elements (I) isolated from the endothelial protein C receptor (EPCR)
promoter which directs expression selectively to endothelial cells are new. Also claimed are
constructs for heterologous gene expression comprising (I), USE - The regulatory elements
are useful to control expression of a gene/biologically active nucleotide molecule
(claimed), by expressing these under control of one of the elements (optionally with the
thrombin response element) (claimed). Expression of the gene/nucleotide molecule is
selectively in large vessel endothelial cells and/or as a result of environmental stimuli
(either thrombin or serum) can be achieved by inclusion of the appropriate

regulatory
element(s). Atherosclerosis and most other vascular diseases primarily occur in large
vessels, and for gene therapy for such diseases it is desirable to target endothelial cells,
the primary defence mechanism against cellular infiltration and thrombosis. The constructs
are therefore particularly useful in gene therapy, especially when the gene encodes a
protein, or the nucleotide molecules are antisense, triplex forming, ribozymes or guide
sequences for RNAase P (claimed) which are used to mutate or stop transcription of a
particular gene. Such genes/nucleotide molecules may be expressed in vivo in patients or in
cell culture (claimed). For example, endothelial response elements may be used for any gene
therapy where systemic distribution is required, whilst large vessel endothelial cell
response elements are useful for expression of thrombomodulin in large vessel endothelium to
decrease clot propensity at atheromas or in autoimmune diseases; the environmental stimuli
response element(s) are useful e.g. to deliver agents whose expression should be increased
during increased thrombin/platelet activation or regional trauma. The regulatory elements
are also useful as hybridisation probes, in increasing expression of recombinant proteins by
exposure of the encoding construct to thrombin and in drug screening and design (not
claimed).

L5: Entry 14 of 15
File: DWPI
May 11, 2000

DERWENT-ACC-NO: 1998-286871
DERWENT-WEEK: 200031

TITLE: Regulatory elements from the endothelial protein C receptor promoter - useful to direct
expression of genes or nucleotide molecules e.g. to endothelial cells or only large vessel
endothelial cells in gene therapy

ABTX:
Regulatory elements (I) isolated from the endothelial protein C receptor (EPCR) promoter which
directs expression selectively to endothelial cells are new. Also claimed are constructs for
heterologous gene expression comprising (I)

15. Document ID: AU 707349 B, WO 9605303 A1, AU 9532723 A, EP 777731 A1, US 5695993 A, US 5852171 A

L5: Entry 15 of 15
File: DWPI
Jul 8, 1999

DERWENT-ACC-NO: 1996-139699
DERWENT-WEEK: 199938

TITLE: Isolated endothelial cell protein C/activated protein C receptor - used to inhibit
inflammatory responses, screen for cpds. which alter receptor binding and, by blocking receptor
binding, enhance inflammatory response

PRIORITY-DATA: 1994US-0289699 (August 12, 1994), 1997US-0878283 (June 18, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 707349 B	July 8, 1999	N/A	000	C12N015/12
WO 9605303 A1	February 22, 1996	E	058	C12N015/12
AU 9532723 A	March 7, 1996	N/A	000	C12N015/12
EP 777731 A1	June 11, 1997	E	000	C12N015/12
US 5695993 A	December 9, 1997	N/A	028	C12N005/16
US 5852171 A	December 22, 1998	N/A	000	C07K014/705

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 707349B	August 9, 1995	1995AU-0032723	N/A
AU 707349B		AU 9532723	Previous Publ.
AU 707349B		WO 9605303	Based on
WO 9605303A1	August 9, 1995	1995WO-US09636	N/A
AU 9532723A	August 9, 1995	1995AU-0032723	N/A
AU 9532723A		WO 9605303	Based on
EP 777731A1	August 9, 1995	1995EP-0929335	N/A
EP 777731A1	August 9, 1995	1995WO-US09636	N/A
EP 777731A1		WO 9605303	Based on

US 5695993A
August 12, 1994
1994US-0289699
N/A
US 5852171A
August 12, 1994
1994US-0289699
Div ex
US 5852171A
June 18, 1997
1997US-0878283
N/A
US 5852171A
US 5695993
Div ex

INT-CL (IPC): A61K 38/17; A61K 39/395; C07H 21/04; C07K 14/705; C07K 16/28; C12N 5/16; C12N 15/11; C12N 15/12; G01N 33/68

IN: ESMON, C T, FUKUDOME, K

AB: Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new.
Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours., Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours., Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours.

L5: Entry 15 of 15
File: DWPI
Jul 8, 1999

DERWENT-ACC-NO: 1996-139699
DERWENT-WEEK: 199938

TITLE: Isolated endothelial cell protein C/activated protein C receptor - used to inhibit inflammatory responses, screen for cpds. which alter receptor binding and, by blocking receptor binding, enhance inflammatory response

ABTX:
Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR.

ABEQ:
Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR.

ABEQ:
Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR.

1. Document ID: US 6120989 A

L7: Entry 1 of 44
File: USPT
Sep 19, 2000

US-PAT-NO: 6120989
DOCUMENT-IDENTIFIER: US 6120989 A
TITLE: Isolated human cytomegalovirus polypeptides and uses thereof
DATE-ISSUED: September 19, 2000

US-CL-CURRENT: 435/5; 424/185.1, 424/192.1, 424/230.1, 435/69.1, 435/69.3, 435/7.92, 435/7.94, 435/975, 530/324, 530/328 , 536/23.72, 930/220

APPL-NO: 8/ 506553
DATE FILED: July 25, 1995

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY

APPL-NO APPL-DATE

DE 44 26 453 July 26, 1994

DE 44 35 789 October 6, 1994

IN: Vornhagen; Rolf, Hinderer; Walter, Sonneborn; Hans-H., Plachter; Bodo, Jahn; Gerhard ,

AB: Diagnostically relevant polypeptides and fusion proteins comprising an amino acid sequence which originates from cytomegalovirus and corresponds to a region of the major DNA-binding protein or of the C-terminal region of the tegument protein pp150 fused with at least one further fragment from another antigenic protein of cytomegalovirus are disclosed. The major DNA-binding protein is encoded by the reading frame UL57. The poly-peptides and fusion proteins according to the invention can be used in an advantageous manner in diagnostic tests and methods for the detection of IgM antibodies against cytomegalovirus.

L7: Entry 1 of 44 File: USPT Sep 19, 2000

DOCUMENT-IDENTIFIER: US 6120989 A
TITLE: Isolated human cytomegalovirus polypeptides and uses thereof

ABPL:
Diagnostically relevant polypeptides and fusion proteins comprising an amino acid sequence which originates from cytomegalovirus and corresponds to a region of the major DNA-binding protein or of the C-terminal region of the tegument protein pp150 fused with at least one further fragment from another antigenic protein of cytomegalovirus are disclosed. The major DNA-binding protein is encoded by the reading frame UL57. The poly-peptides and fusion proteins according to the invention can be used in an advantageous manner in diagnostic tests and methods for the detection of IgM antibodies against cytomegalovirus.

2. Document ID: US 5916874 A

L7: Entry 2 of 44 File: USPT Jun 29, 1999

US-PAT-NO: 5916874
DOCUMENT-IDENTIFIER: US 5916874 A
TITLE: Method for treating liver injury
DATE-ISSUED: June 29, 1999

US-CL-CURRENT: 514/12; 530/350, 530/380, 530/381

APPL-NO: 8/ 733564
DATE FILED: October 18, 1996

PARENT-CASE:
This application is a continuation-in-part of PCT Application No. PCT/JP95/00704, filed on Apr. 10, 1995, which designated the United States and on which priority is claimed under 35 U.S.C. .sctn. 120.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY APPL-NO APPL-DATE

JP 6-081196 April 20, 1994

IN: Fujiwara; Kenji, Mochida; Satoshi

AB: Disclosed is a method for treating liver injury caused by microorganism or toxic substance, which comprises administering to a patient suffering from liver injury a composition comprising a thrombomodulin, which has the ability to bind to thrombin and promote the activation of protein C by thrombin, as an active ingredient and at least one pharmaceutically acceptable carrier. The method of the present invention is very effective for ameliorating liver injury, such as fulminant hepatitis and hepatic veno-occlusive disease (VOD) which is likely to frequently occur after bone marrow transplantation.

L7: Entry 2 of 44 File: USPT Jun 29, 1999

DOCUMENT-IDENTIFIER: US 5916874 A
TITLE: Method for treating liver injury

ABPL:
Disclosed is a method for treating liver injury caused by microorganism or toxic substance, which comprises administering to a patient suffering from liver injury a composition comprising a thrombomodulin, which has the ability to bind to thrombin and promote the activation of protein C by thrombin, as an active ingredient and at least one pharmaceutically acceptable carrier. The method of the present invention is very effective for ameliorating liver injury, such as fulminant hepatitis and hepatic veno-occlusive disease (VOD) which is likely to frequently occur after bone marrow transplantation.

CLPR:
1. A method for ameliorating liver injury due to fulminant hepatitis or hepatic veno-occlusive disease in a patient which comprises administering to a patient in need thereof an effective amount of thrombomodulin to suppress the serum level of glutamic pyruvic transaminase and bilirubin, wherein said thrombomodulin has the ability to bind to thrombin and promote the activation of protein C by thrombin, and wherein said thrombomodulin is soluble thrombomodulin which lacks a transmembrane domain or which is surfactant-treated thrombomodulin which contains a transmembrane domain.

3. Document ID: US 5852171 A

L7: Entry 3 of 44

File: USPT

Dec 22, 1998

US-PAT-NO: 5852171
DOCUMENT-IDENTIFIER: US 5852171 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor
DATE-ISSUED: December 22, 1998

US-CL-CURRENT: 530/350; 530/380

APPL-NO: 8/ 878283
DATE FILED: June 18, 1997

PARENT-CASE:
This is a divisional of U.S. Ser. No. 08/289,699, filed on Aug. 12, 1994, now U.S. Pat. No. 5,695,993.

,IN: Fukudome; Kenji, Esmon; Charles T.

AB: Human protein C and activated protein C were shown to bind to endothelium specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+ dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I transmembrane glycoprotein capable of binding protein C. This protein appears to be a member of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell protein C receptor (EPCR) function and message are both down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the CD1/MHC superfamily provides insights into the role of protein C in regulating the inflammatory response, and determination of methods for pharmaceutical use in manipulating the inflammatory response.

L7: Entry 3 of 44

File: USPT

Dec 22, 1998

DOCUMENT-IDENTIFIER: US 5852171 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

DEPR:
As described herein, a variety of compounds can be used to inhibit or enhance expression of the EPCR. The nature of the disorder will determine if the expression should be enhanced or inhibited. For example, based on the studies involving the use of an anti-protein C antibody in combination with cytokine, it should be possible to treat solid tumors by enhancing an inflammatory response involving blocking of protein C or activated protein C binding to an endothelial cell protein C/activated protein C receptor by administering to a patient in need of treatment thereof an amount of a compound blocking binding of protein C or activated protein C to the receptor. Similarly, it should be possible to treat disorders such as gram negative sepsis, stroke, thrombosis, septic shock, adult respiratory distress syndrome, and pulmonary emboli using a method for inhibiting an inflammatory response involving administration of EPCR or EPCR fragments or substances that upregulate EPCR expression to a patient in need of treatment therof.

4. Document ID: US 5830448 A

L7: Entry 4 of 44

File: USPT

Nov 3, 1998

US-PAT-NO: 5830448
DOCUMENT-IDENTIFIER: US 5830448 A
TITLE: Compositions and methods for the treatment of tumors
DATE-ISSUED: November 3, 1998

US-CL-CURRENT: 424/85.2; 424/85.1, 424/85.5, 514/2, 530/351, 530/381

APPL-NO: 8/ 470777
DATE FILED: June 6, 1995

PARENT-CASE:
This is a divisional of application Ser. No. 08/260,850 filed on 16 Jun. 1994, which application is incorporated herein by reference and to which application priority is claimed under 35 USC .sctn.120.

IN: Vehar; Gordon A.

AB: The invention concerns a method for inhibiting the growth and/or causing regression of tumors by administering a therapeutically effective dose of a procoagulant and a cytokine, preferably TNF-.beta., TNF-.alpha. and/or IL-1. In a specific aspect, the invention concerns a method for tumor treatment by the administration of a therapeutically effective amount of a thrombomodulin inhibitor and a cytokine. The invention also concerns thrombomodulin inhibitors and pharmaceutical compositions used in the course of these treatments.

L7: Entry 4 of 44

File: USPT

Nov 3, 1998

DOCUMENT-IDENTIFIER: US 5830448 A
TITLE: Compositions and methods for the treatment of tumors

DEPR:
The treatment of the present invention may be combined with known tumor therapies, such as radiation therapy, chemotherapy, and immunotoxin therapy, including the administration of immunotoxin directed against the tumor vasculature as described by Burrows and Thorpe, supra.
Most preferably, the treatment of the present invention is combined with the administration of a (further) inhibitor of the protein C system, which may, for example, be antibodies to protein C or activated protein, C, antibodies to protein S, inactivated protein C and C4b binding protein, as described in U.S. Pat. No. 5,147,638. In addition, steroids or other agents known to reduce or prevent platelet loss may be administered prior to, during or after

treatment.

5. Document ID: US 5827824 A

L7: Entry 5 of 44

File: USPT

Oct 27, 1998

US-PAT-NO: 5827824
DOCUMENT-IDENTIFIER: US 5827824 A
TITLE: Protease-resistant thrombomodulin analogs
DATE-ISSUED: October 27, 1998

US-CL-CURRENT: 514/12; 514/822, 530/380, 530/402, 530/412, 530/419

APPL-NO: 8/ 463605
DATE FILED: June 5, 1995

PARENT-CASE:
This application is a division of U.S. application Ser. No. 08/197,576, filed Feb. 16, 1994, which is a continuation of U.S. application Ser. No. 07/830,577, filed Feb. 5, 1992, now abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/568,456, filed Aug. 15, 1990 abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/506,325, filed Apr. 9, 1990, now U.S. Pat. No. 5,256,770, which is a continuation-in-part of U.S. application Ser. No. 07/406,941, filed Sep. 13, 1989, now abandoned, which is a continuation-in-part of U.S. application Ser. No. 07/345,372, filed Apr. 28, 1989, now abandoned, all of whose disclosures are entirely incorporated by reference herein. This application also claims foreign priority from the PCT application Ser. No. 90/00955, filed Feb. 16, 1990, which became U.S. application Ser. No. 07/730,975, filed Jul. 29, 1991, now abandoned, which claims priority from U.S. application Ser. No. 07/406,941, filed Sep. 13, 1989 abandoned, which was a continuation-in-part of U.S. application Ser. No. 07/345,372, filed Apr. 28, 1989, now abandoned, which was a continuation-in-part of U.S. application Ser. No. 07/312,141, filed Feb. 17, 1989, now abandoned.

IN: Light; David Richard, Andrews; William H., Clarke; Jeffrey Homer, Wydro; Robert Michael, Young; Patricia Ann

AB: The present invention relates to the single-chain thrombomodulin ("TM") and analogs thereof that are not susceptible to cleavage by proteases and retain the biological activity of thrombomodulin, as well as methods of use in, for example, antithrombotic therapy. Novel proteins, nucleic acid gene sequences, pharmaceuticals and methods of inhibiting thrombotic activity are disclosed.

L7: Entry 5 of 44

File: USPT

Oct 27, 1998

DOCUMENT-IDENTIFIER: US 5827824 A
TITLE: Protease-resistant thrombomodulin analogs

CLPR:
2. A method of treating thrombotic disease, comprising administering an effective amount of a thrombomodulin protein analog, wherein the amino acid sequence of the N-terminus is modified by substitution or deletion of one or more amino acids at the N-terminus to prevent signal sequence cleavage heterogeneity, whereby the analog has a single N-terminus, and wherein the analog has at least 50% of the ability to potentiate thrombin-mediated activation of protein C as said protein having a native thrombomodulin N-terminus wherein said analog comprises a polypeptide having an amino acid sequence corresponding to the lectin binding, EGF and O-linked glycosylation domains of native thrombomodulin.

6. Document ID: US 5762921 A

L7: Entry 6 of 44

File: USPT

Jun 9, 1998

US-PAT-NO: 5762921
DOCUMENT-IDENTIFIER: US 5762921 A
TITLE: Composition and methods for the treatment of tumors
DATE-ISSUED: June 9, 1998

US-CL-CURRENT: 424/85.1; 424/158.1, 424/198.1, 424/85.2, 424/85.5, 514/12, 530/350, 530/351, 530/381

APPL-NO: 8/ 594360
DATE FILED: January 30, 1996

PARENT-CASE:
This is a continuation of application Ser. No. 08/260,850 filed on 16 Jun. 1994 (now abandoned), which application(s) is(are) incorporated herein by reference and to which application(s) priority is claimed under 35 USC .sctn. 120.

IN: Vehar; Gordon A.

AB: The invention concerns a method for inducing a selective collapse of the vasculature of a solid tumor by administering to a patient a therapeutically effective dose of a combination of a compound preventing the formation of a functional thrombin-thrombomodulin complex and a cytokine selected from the group of TNF-.beta. (LT), TNF-.alpha., IL-1, and IFN-.gamma.. The invention further concerns the composition used in this method.

L7: Entry 6 of 44

File: USPT

Jun 9, 1998

DOCUMENT-IDENTIFIER: US 5762921 A
TITLE: Composition and methods for the treatment of tumors

DEPR:
The treatment of the present invention may be combined with known tumor therapies, such as radiation therapy, chemotherapy, and immunotoxin therapy, including the

administration of
immunotoxin directed against the tumor vasculature as described by Burrows and Thorpe, supra.
Most preferably, the treatment of the present invention is combined with the administration of a
(further) inhibitor of the protein C system which may, for example, be antibodies to protein C or
activated protein, C, antibodies to protein S, inactivated protein C and C4b binding protein, as
described in U.S. Pat. No. 5,147,638. In addition, steroids or other agents known to reduce or
prevent platelet loss may be administered prior to, durina or after treatment.

7. Document ID: US 5695993 A

L7: Entry 7 of 44
File: USPT
Dec 9, 1997

US-PAT-NO: 5695993
DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor
DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 435/325; 435/320.1, 435/69.1, 536/23.5

APPL-NO: 8/ 289699
DATE FILED: August 12, 1994

IN: Fukudome; Kenji, Esmon; Charles T.

AB: Human protein C and activated protein C were shown to bind to endothelium
specifically, selectively and saturably (Kd=30 nM, 7000 sites per cell) in a Ca.sup.2+
dependent fashion. Expression cloning revealed a 1.3 kb CDNA that coded for a novel type I
transmembrane glycoprotein capable of binding protein C. This protein appears to be a member
of the CD1/MHC superfamily. Like thrombomodulin, the receptor involved in protein C
activation, the endothelial cell protein C receptor (EPCR) function and message are both
down regulated by exposure of endothelium to TNF. Identification of EPCR as a member of the
CD1/MHC superfamily provides insights into the role of protein C in regulating the
inflammatory response, and determination of methods for pharmaceutical use in manipulating
the inflammatory response.

L7: Entry 7 of 44
File: USPT
Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695993 A
TITLE: Cloning and regulation of an endothelial cell protein C/activated protein C receptor

DEPR:
As described herein, a variety of compounds can be used to inhibit or enhance expression of the
EPCR. The nature of the disorder will determine if the expression should be enhanced or
inhibited. For example, based on the studies involving the use of an anti-protein C antibody in
combination with cytokine, it should be possible to treat solid tumors by enhancing an
inflammatory response involving blocking of protein C or activated protein C binding to an
endothelial cell protein C/activated protein C receptor by administering to a patient in need of
treatment thereof an amount of a compound blocking binding of protein C or activated protein C to
the receptor. Similarly, it should be possible to treat disorders such as gram negative sepsis,
stroke, thrombosis, septic shock, adult respiratory distress syndrome, and pulmonary emboli using
a method for inhibiting an inflammatory response involving administration of EPCR or EPCR
fragments or substances that upregulate EPCR expression to a patient in need of treatment therof.

8. Document ID: US 5695964 A

L7: Entry 8 of 44
File: USPT
Dec 9, 1997

US-PAT-NO: 5695964
DOCUMENT-IDENTIFIER: US 5695964 A
TITLE: Recombinant DNA vectors, including plasmids, and host cells for production of truncated
thrombomodulin
DATE-ISSUED: December 9, 1997

US-CL-CURRENT: 435/69.6; 435/243, 435/320.1, 435/325, 435/358

APPL-NO: 8/ 587389
DATE FILED: January 17, 1996

PARENT-CASE:
This is a Division of application Ser. No. 08/307,444 filed Sep. 19, 1994, now issued as U.S.
Pat. No. 5,516,659, which in turn is a Continuation of application Ser. No. 07/835,436 filed Mar.
27, 1992, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
JP
Hei 2-168766
June 27, 1990

IN: Nii; Atsushi, Morishita; Hideaki, Uemura; Akio, Mochida; Ei

AB: This invention relates to novel vectors and host cells containing nucleic acids
coding for a polypeptide having thrombin binding ability, anticoagulant activity and
thrombolytic activity. The polypeptide can be efficiently produced in large quantities by
means of genetic recombination techniques using the vectors and host cells of the present
invention. Since the polypeptide exhibits anticoagulant activity and thrombolytic activity
without generating side effects such as bleeding tendencies, it can be applied effectively
to the prevention and treatment of hypercoagulability-related diseases.

L7: Entry 8 of 44

File: USPT

Dec 9, 1997

DOCUMENT-IDENTIFIER: US 5695964 A
TITLE: Recombinant DNA vectors, including plasmids, and host cells for production of truncated
thrombomodulin

DEPR:
The polypeptide of the present invention imparts an effect of inhibiting both blood coagulation
and platelet aggregation because of its function to bind to thrombin and inactivate the activity
thereof and, at the same time, exhibits anticoagulant and thrombolytic activities by activating
protein C. Because of such effects, it is possible to use the polypeptide for the treatment of a
broad range of hypercoagulability-related diseases, based on its thrombus formation inhibiting
activity, thrombolytic activity, anti-DIC activity and the like. Especially, reduction of side
effects can be expected because of its excellent function to activate protein C.

9. Document ID: US 5545721 A

L7: Entry 9 of 44

File: USPT

Aug 13, 1996

US-PAT-NO: 5545721
DOCUMENT-IDENTIFIER: US 5545721 A
TITLE: Conjugates for the prevention and treatment of sepsis
DATE-ISSUED: August 13, 1996

US-CL-CURRENT: 530/391.7; 530/300, 530/317, 530/319, 530/322, 530/345, 530/350, 530/391.1,
530/391.5, 530/391.9, 530/402

APPL-NO: 8/ 169701
DATE FILED: December 17, 1993

PARENT-CASE:
RELATED APPLICATION DATA This Application is a Continuation-in-Part Application of application
Ser. No. 07/995,388, filed on Dec. 21, 1992, now abandoned.

IN: Carroll; Sean B., Firca; Joseph R., Pugh; Charles, Padhye; Nisha V.

AB: Compositions and methods are described for preventing and treating sepsis in
humans and other animals. Surgical patients, low birth weight infants, burn and trauma
victims, as well as other individuals at risk can be treated prophylactically. Methods for
treating acute infections with advantages over current therapeutic approaches are provided.
Conjugates and methods of making conjugates for the prevention and treatment of sepsis are
described.

L7: Entry 9 of 44

File: USPT

Aug 13, 1996

DOCUMENT-IDENTIFIER: US 5545721 A
TITLE: Conjugates for the prevention and treatment of sepsis

BSPR:
The present invention contemplates a method of treatment, comprising: (a) providing a mammal for
treatment; (b) providing a therapeutic preparation, comprising an endotoxin-binding compound
covalently bound to protein; and (c) administering the preparation to the mammal (e.g.,
intravenous). The endotoxin-binding compound may be polymyxin and the protein is preferably
non-specific immunoglobulin such as IgG.

10. Document ID: US 5516659 A

L7: Entry 10 of 44

File: USPT

May 14, 1996

US-PAT-NO: 5516659
DOCUMENT-IDENTIFIER: US 5516659 A
TITLE: Truncated thrombomodulin, recombinant production thereof, and therapeutic agent
DATE-ISSUED: May 14, 1996

US-CL-CURRENT: 435/69.6; 514/2, 514/8, 530/350, 530/395, 536/23.5

APPL-NO: 8/ 307444
DATE FILED: September 19, 1994

PARENT-CASE:
This is a continuation of application Ser. No. 07/835,436 filed Mar. 27, 1992, now abandoned.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY APPL-NO APPL-DATE
JP 2-168766 June 27, 1990

IN: Nii; Atsushi, Morishita; Hideaki, Uemura; Akio, Mochida; Ei

AB: This invention relates to a novel polypeptide which is obtained by means of
genetic recombination DNA techniques and has thrombin binding ability, anticoagulant
activity and thrombolytic activity. The polypeptide of the present invention can be produced
in a large quantity and efficiently by means of genetic recombination techniques. Since the
polypeptide of the present invention exhibits anticoagulant activity and thrombolytic
activity without generating side effects such as bleeding tendency, it can be applied
effectively to the prevention and treatment of hypercoagulability-related diseases.

L7: Entry 10 of 44

File: USPT

May 14, 1996

DOCUMENT-IDENTIFIER: US 5516659 A
TITLE: Truncated thrombomodulin, recombinant production thereof, and

therapeutic agent

DEPR:
The polypeptide of the present invention imparts an effect of inhibiting both blood coagulation
and platelet aggregation because of its function to bind to thrombin and inactivate the activity
thereof and, at the same time, exhibits anticoagulant and thrombolytic activities by activating
protein C. Because of such effects, it is possible to use the polypeptide for the treatment of a
broad range of hypercoagulability-related diseases, based on its thrombus formation inhibiting
activity, thrombolytic activity, anti-DIC activity and the like. Especially, reduction of side
effects can be expected because of its excellent function to activate protein C.

11. Document ID: US 5254532 A

L7: Entry 11 of 44
File: USPT
Oct 19, 1993

US-PAT-NO: 5254532
DOCUMENT-IDENTIFIER: US 5254532 A
TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use
of such a preparation and a method of producing the same
DATE-ISSUED: October 19, 1993

US-CL-CURRENT: 514/2; 514/12, 514/21, 514/8

DISCLAIMER DATE: 20090901
APPL-NO: 7/ 840719
DATE FILED: February 21, 1992

PARENT-CASE:
This application is a continuation of application Ser. No. 07/540,357, filed on Jun. 19, 1990,
now U.S. Pat. No. 5,143,901.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
AT
1551/89
June 26, 1989

IN: Schwarz; Hans P., Molinari; Ewald, Linnau; Yendra, Pfeiler; Susanne

AB: A preparation for the treatment and prevention of thromboses and thromboembolic
complications is disclosed, which preparation has a content of protein S at a concentration
at least 50 times that present in native plasma and is free from C4b-binding protein,
optionally in combination with a content of activated protein C.

L7: Entry 11 of 44
File: USPT
Oct 19, 1993

DOCUMENT-IDENTIFIER: US 5254532 A

TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use
of such a preparation and a method of producing the same

ABPL:
A preparation for the treatment and prevention of thromboses and thromboembolic complications is
disclosed, which preparation has a content of protein S at a concentration at least 50 times that
present in native plasma and is free from C4b-binding protein, optionally in combination with a
content of activated protein C.

BSPR:
To obtain this object, the invention provides prepartion for treating and preventing thromboses
and thromboembolic complications, having a protein S content in a concentration that is at least
50 times that of native plasma and being free from C4b-binding protein optionally in combination
with a content of activates protein C.

12. Document ID: US H001148 H

L7: Entry 12 of 44
File: USPT
Mar 2, 1993

US-PAT-NO: H001148
DOCUMENT-IDENTIFIER: US H001148 H
TITLE: Method of separating activated human protein C
DATE-ISSUED: March 2, 1993

US-CL-CURRENT: 435/13; 435/219, 435/815, 436/548

APPL-NO: 7/ 815870
DATE FILED: January 3, 1992

PARENT-CASE:
This application is a continuation of now abandoned application Ser. No. 07/181,424, filed on
Apr. 14, 1988.

FOREIGN-APPL-PRIORITY-DATA:
COUNTRY
APPL-NO
APPL-DATE
JP
62-93377
April 17, 1987

IN: Wakabayashi; Kenji, Sumi; Yoshihiko, Ichikawa; Yataro, Sakata; Yoichi, Aoki;
Nobuo

AB: A method of separating activated human protein C, which comprises bringing a
mixture containing activated human protein C having a gamma-carboxyglutamic acid (Gla)
domain in the presence of a calcium ion into contact with a fixed antibody comprising an
insoluble carrier and fixed thereto an antibody to a complex of human protein C and a
calcium ion bound to the Gla domain whereby the activated human protein C is captured by the
fixed antibody in the form in which the calcium ion is bound to the Gla domain. A method is
also provided for separating activated human protein C from a mixture

containing human
protein C and activated human protein C, which comprises bringing a first mixture containing
human protein C and activated human protein C having a Gla domain into contact with a first
fixed antibody comprising an insoluble carrier and fixed thereto a first antibody to human
protein C but not to activated human protein C to form a second mixture substantially free
from human protein C while the human protein C is captured by the first fixed antibody, and
bringing the second mixture in the presence of a calcium ion into contact with a second
fixed antibody comprising an insoluble carrier and fixed thereto a second antibody to a
complex of human protein C and a calcium ion bound at the Gla domain, whereby the activated
human protein C is captured by the second fixed antibody in the form in which the calcium
ion is bound to the Gla domain.

L7: Entry 12 of 44 File: USPT Mar 2, 1993

DOCUMENT-IDENTIFIER: US H001148 H
TITLE: Method of separating activated human protein C

CLPR:
1. A method of separating activated human protein C, which has a gamma-carboxyglutamic acid (Gla)
domain and is biologically active, from a mixture containing activated human protein C, which
comprises bringing a mixture containing activated human protein C having a Gla domain in the
presence of calcium into contact with a fixed monoclonal antibody comprising an insoluble carrier
and fixed thereto a monoclonal antibody specific to a human protein C having a calcium ion bound
to the Gla domain, whereby the activated human protein C having a calcium ion bound to the Gla
domain is bound to the fixed monoclonal antibody, and then treating the fixed monoclonal antibody
binding the activated human protein C having the calcium ion bound to its Gla domain with an
aqueous medium substantially free from calcium ions, whereby the activated human protein C is
released from the fixed antibody in a form not binding the calcium ion in the Gla domain.

CLPV:
(2) bringing the second mixture in the presence of calcium into contact with a second fixed
monoclonal antibody comprising an insoluble carrier and fixed thereto a second antibody specific
to human protein C having a calcium ion bound to the Gla domain, whereby the activated human
protein C having a calcium ion bound to the Gla domain is bound to the second fixed monoclonal
antibody, and then treating the second monoclonal antibody, and then treating the second
monoclonal antibody capturing the activated human protein C having the calcium ion bound to its
Gla domain with an aqueous medium substantially free from calcium ions, whereby the activated
human protein C is separated from the second fixed antibody in a form not binding the calcium ion
in the Gla domain.

13. Document ID: US 5143901 A

L7: Entry 13 of 44 File: USPT Sep 1, 1992

US-PAT-NO: 5143901
DOCUMENT-IDENTIFIER: US 5143901 A
TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use
of such a preparation and a method of producing the same
DATE-ISSUED: September 1, 1992

US-CL-CURRENT: 514/2; 514/12, 514/21, 514/8

APPL-NO: 7/ 540357
DATE FILED: June 19, 1990

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
AT	1551/89	June 26, 1989

IN: Schwarz; Hans P., Molinari; Ewald, Linnau; Yendra, Pfeiler; Susanne

AB: A preparation for the treatment and prevention of thromboses and thromboembolic
complications is disclosed, which preparation has a content of protein S at a concentration
at least 50 times that present in native plasma and is free from C4b-binding protein,
optionally in combination with a content of activated protein C.

L7: Entry 13 of 44 File: USPT Sep 1, 1992

DOCUMENT-IDENTIFIER: US 5143901 A
TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use
of such a preparation and a method of producing the same

ABPL:
A preparation for the treatment and prevention of thromboses and thromboembolic complications is
disclosed, which preparation has a content of protein S at a concentration at least 50 times that
present in native plasma and is free from C4b-binding protein, optionally in combination with a
content of activated protein C.

BSPR:
To obtain this object, the invention provides a preparation for treating and preventing
thromboses and thromboembolic complications, having a protein S content in a concentration that
is at least 50 times that of native plasma and being free from C4b-binding protein, optionally in
combination with a content of activated protein C.

14. Document ID: US 4849403 A

L7: Entry 14 of 44

File: USPT

Jul 18, 1989

US-PAT-NO: 4849403
DOCUMENT-IDENTIFIER: US 4849403 A
TITLE: Protein C activator, methods of preparation and use thereof
DATE-ISSUED: July 18, 1989

US-CL-CURRENT: 512/2; 424/542, 435/23, 435/24, 435/68.1, 530/381

APPL-NO: 6/ 861786
DATE FILED: May 9, 1986

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
CH	2267/85	May 29, 1985
CH	4135/84	September 25, 1985
CH	5087/85	November 28, 1985

IN: Stocker; Kurt F., Svendsen; Lars G.

AB: A method and composition for assaying protein C is described. The method comprises reacting a protein C-containing medium with a protein C-activating activator preparation obtained from venom of the snake Agkistrodon contortrix, or venom of another snake species which undergoes an immunological cross-reaction with the venom of Agkistrodon contortrix, to cause maximum activation of protein C and subsequently determining the quantity of activated protein C, said quantity being proportional to the amount of protein C in said medium. Also disclosed is a method and composition for treating thrombotic disorders with the activator preparation and a method of obtaining the activator preparation by culturing of a cloned microorganism.

L7: Entry 14 of 44

File: USPT

Jul 18, 1989

DOCUMENT-IDENTIFIER: US 4849403 A
TITLE: Protein C activator, methods of preparation and use thereof

BSPR:
The activator preparation of the invention may also be obtained by dilution of the snake venom in an aqueous medium, removal of the undesired venom components from the solution either by fractionated alcohol precipitation, fractionated salt precipitation or heat treatment at an acid pH for the purpose of preparing a pre-purified venom fraction, further purification of the obtained pre-purified venom fraction by chromatography on an anion exchanger having the appropriate porosity for binding proteins, e.g. cross-linked diethylaminoethyldextran or diethylaminoethylcellulose, elution with sodium phosphate buffer at neutral pH and increasing ionic strength, further chromatography on a cation exchanger, e.g. cross-linked carboxymethyldextran or carboxymethylcellulose, elution with a sodium acetate buffer at an acid pH, concentration of the protein C-activating eluates by ultrafiltration, removal of electrolytes and final purification of the concentrate by chromatography on a molecular sieve gel, e.g. a cross-linked dextran gel, using diluted aqueous acetic acid as the eluent, and subsequent lyophilization.

BSPR:
Fresh, frozen or lyophilized blood plasma from men or mammals comprising the usual calcium ion-binding additives, such as citrate or oxalate, or plasma preparations from which inhibitors or components irrelevant to the protein C assay were removed by heating, pH adjustment or treatment with enzymes, adsorbing or protein-precipitating agents, can be used as natural substrates for measuring the action of activated protein C via inactivation of factors V and VIII in the clotting test. In addition, clotting factor concentrates from blood plasma or by-products thereof, which are applied for therapeutical purposes, and factor-deficient plasma can be used as well.

15. Document ID: US 4638050 A

L7: Entry 15 of 44

File: USPT

Jan 20, 1987

US-PAT-NO: 4638050
DOCUMENT-IDENTIFIER: US 4638050 A
TITLE: Thrombin-binding substance and process for its production
DATE-ISSUED: January 20, 1987

US-CL-CURRENT: 530/413; 424/583, 530/350, 530/399, 530/851

APPL-NO: 6/ 713821
DATE FILED: March 20, 1985

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
JP	59-55792	March 23, 1984

IN: Aoki; Nobuo, Kurosawa; Shinichiro

AB: A thrombin-binding substance derived from human tissue and having the characteristics of (a) molecular weight: 88,000.+-.20,000 in reduced condition and 71,000.+-.20,000 in unreduced condition; (b) isoelectric point: .sub.p H 4.2.+-.0.5; (c) affinity: strong for thrombin; (d) activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging clotting time; and (e) stability: stable over a .sub.p H range of 2 to 10 and stable to denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively useful for thrombolysis and anticoagulation.

L7: Entry 15 of 44

File: USPT

Jan 20, 1987

DOCUMENT-IDENTIFIER: US 4638050 A
TITLE: Thrombin-binding substance and process for its production

ABPL:
A thrombin-binding substance derived from human tissue and having the characteristics of (a)
molecular weight: 88,000.+-.20,000 in reduced condition and 71,000.+-.20,000 in unreduced
condition; (b) isoelectric point: .sub.p H 4.2.+-.0.5; (c) affinity: strong for thrombin; (d)
activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging
clotting time; and (e) stability: stable over a .sub.p H range of 2 to 10 and stable to
denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively
useful for thrombolysis and anticoagulation.

16. Document ID: US 4259357 A

L7: Entry 16 of 44

File: USPT

Mar 31, 1981

US-PAT-NO: 4259357
DOCUMENT-IDENTIFIER: US 4259357 A
TITLE: Stabilized milkproteins-containing compositions
DATE-ISSUED: March 31, 1981

US-CL-CURRENT: 426/42; 426/56, 426/623, 426/63, 426/630, 426/634, 426/635, 426/641, 426/807

APPL-NO: 6/ 043512
DATE FILED: May 29, 1979

FOREIGN-APPL-PRIORITY-DATA:

COUNTRY	APPL-NO	APPL-DATE
GB	25165/78	May 31, 1978

IN: Van Kranenburg; Simon

AB: A process for stabilizing an aqueous composition, which contains insoluble
components mainly consisting of insoluble protein, insoluble carbohydrates and fats, which
tend either to precipitate or to migrate to the surface of the composition, which process
comprises incorporating into a dry composition a stabilizing proportion of a casein which
has been enzymatically hydrolysed under conditions such that the K-casein moiety has been
hydrolysed whereas no peptides having a molecular weight below 10.sup.4 have been formed.

L7: Entry 16 of 44

File: USPT

Mar 31, 1981

DOCUMENT-IDENTIFIER: US 4259357 A
TITLE: Stabilized milkproteins-containing compositions

CLPR:
1. A process for producing a dry composition, which on dilution with water yields a homogenous
aqueous composition, said process for producing said dry composition comprising; admixing (a)
from 10 to 30 wt. % fat, (b) from 10 to 30 wt % protein, (c) from 10 to 50 wt. % carbohydrates
said composition having at least part of the protein and the carbohydrates water-insoluble, (d)
at least 0.5 wt. % of a casein stabilizer which has been treated with an effective amount of a
proteolytic enzyme under conditions such that the K-casein moiety contained in said casein is
hydrolysed without forming peptides having a molecular weight of below 10.sup.4 and (e) from 0.1
to 10 wt. %, based on the amount of protein, of a water-soluble or water-dispersible salt which
binds calcium and magnesium ions.

CLPR:
20. A dry composition, which upon dilution with water yields a homogeneous aqueous animal feed
composition, said dry composition comprising (a) from 10 to 30 wt. % fat, (b) from 10 to 30 wt. %
protein, (c) from 10 to 50 wt. % carbohydrates said composition having at least part of the
protein and the carbohydrates water-insoluble, (d) at least 0.5 wt. % of a casein stabilizer
which has been treated with an effective amount of a proteolytic enzyme under conditions such
that the K-casein moiety contained in said casein is hydrolysed without forming peptides having a
molecular weight below 10.sup.4, or at least 0.5 wt. % of untreated casein containing K-casein
and an effective amount of a proteolytic enzyme selected from the group consisting of rennet and
rennet substitutes, and (e) from 0.1 to 10 wt. %, based on the amount of protein, of a
water-soluble or water-dispersible salt which binds calcium and magnesium ions.

17. Document ID: JP 08291193 A

L7: Entry 17 of 44

File: JPAB

Nov 5, 1996

PUB-NO: JP408291193A
DOCUMENT-IDENTIFIER: JP 08291193 A
TITLE: MEDICINAL COMPOSITION CONTAINING PEPTIDE HAVING ACTION PROMOTING ACTIVATION OF PROTEIN C BY THROMBIN

PUBN-DATE: November 5, 1996

INT-CL (IPC): C07H 21/04; A61K 38/00; C12N 15/09; C12P 21/02

APPL-NO: JP08138587
APPL-DATE: May 31, 1996

IN: YAMAMOTO, SHUJI, SUZUKI, KOJI

AB: PURPOSE: To obtain a medicinal composition for treating circulatory diseases,
etc., by blending a peptide capable of promoting activation of a protein C

by thrombin and
having action of antiblood coagulation, suppression of platelet agglutination, thrombolysis,
etc., with an administrable carrier for medicines., CONSTITUTION: This medicine composition
for controlling blood coagulation and platelet agglutination is obtained by blending a
peptide having action binding to thrombin and promoting activation of protein C by thrombin
and having a partial arrangement of amino acid sequence capable of coding DNA derived from
human and having a restriction enzyme site expressed by a restriction enzyme map of the
formula and having all of antiblood coagulation action, platelet agglutination suppression
action and thrombolytic action, almost free from adverse effect and useful as a treating
medicine for circulatory diseases, etc., with one or more kinds of carriers among
saccharide, purified gelatin, albumin, mannitol, glucose and sodium chloride which are
administrable as medicines and preparing the blend., COPYRIGHT: (C)1996,JPO

L7: Entry 17 of 44

File: JPAB

Nov 5, 1996

DOCUMENT-IDENTIFIER: JP 08291193 A
TITLE: MEDICINAL COMPOSITION CONTAINING PEPTIDE HAVING ACTION PROMOTING ACTIVATION OF PROTEIN C BY THROMBIN

FPAR:
CONSTITUTION: This medicine composition for controlling blood coagulation and platelet
agglutination is obtained by blending a peptide having action binding to thrombin and promoting
activation of protein C by thrombin and having a partial arrangement of amino acid sequence
capable of coding DNA derived from human and having a restriction enzyme site expressed by a
restriction enzyme map of the formula and having all of antiblood coagulation action, platelet
agglutination suppression action and thrombolytic action, almost free from adverse effect and
useful as a treating medicine for circulatory diseases, etc., with one or more kinds of carriers
among saccharide, purified gelatin, albumin, mannitol, glucose and sodium chloride which are
administrable as medicines and preparing the blend.

18. Document ID: JP 08027200 A

L7: Entry 18 of 44

File: JPAB

Jan 30, 1996

PUB-NO: JP408027200A
DOCUMENT-IDENTIFIER: JP 08027200 A
TITLE: FUSED PROTEIN

PUBN-DATE: January 30, 1996

INT-CL (IPC): C07K 19/00; C07K 14/435; C12N 9/02; C12N 15/09; C12P 21/02; C12Q 1/66; G01N 33/53; G01N 33/535; C12Q 1/68

APPL-NO: JP06165223
APPL-DATE: July 18, 1994

IN: SUZUKI, EIJI, UEDA, HIROSHI, KAZAMI, JUN, KONO, HAJIME

AB: PURPOSE: To obtain a fused protein capable of being simply mixed with IgG to
label the IgG and useful as a labeled enzyme used for luminescent immunoassay methods, etc.,
by binding a peptide containing an IgG-recognizing region to the end of Cypridina luciferase
by a genetic engineering method., CONSTITUTION: The new fused protein capable of being
simply mixed with IgG to label the IgG with Cypridina luciferase without requiring a
chemical treatment for the labeling and useful as a labeling enzyme for luminescent
immunoassay methods is obtained by binding a peptide containing a region recognizing the IgG
Fc part of a protein A originated from Staphylococcus aureus, a peptide containing a region
recognizing the IgG Fc part of a protein C originated from a streptococcus, etc., to the
amino end of the Cypridina luciferase. The fused protein is obtained by expressing a vector
which is produced by binding the gene of a peptide having a region recognizing the IgG to
the 5'-site of Cypridina luciferase gene through a linker., COPYRIGHT: (C)1996,JPO

L7: Entry 18 of 44

File: JPAB

Jan 30, 1996

DOCUMENT-IDENTIFIER: JP 08027200 A
TITLE: FUSED PROTEIN

FPAR:
CONSTITUTION: The new fused protein capable of being simply mixed with IgG to label the IgG with
Cypridina luciferase without requiring a chemical treatment for the labeling and useful as a
labeling enzyme for luminescent immunoassay methods is obtained by binding a peptide containing a
region recognizing the IgG Fc part of a protein A originated from Staphylococcus aureus, a
peptide containing a region recognizing the IgG Fc part of a protein C originated from a
streptococcus, etc., to the amino end of the Cypridina luciferase. The fused protein is obtained
by expressing a vector which is produced by binding the gene of a peptide having a region
recognizing the IgG to the 5'-site of Cypridina luciferase gene through a linker.

19. Document ID: WO 9534652 A1

L7: Entry 19 of 44

File: EPAB

Dec 21, 1995

PUB-NO: WO009534652A1
DOCUMENT-IDENTIFIER: WO 9534652 A1
TITLE: CALCIUM BINDING RECOMBINANT ANTIBODY AGAINST PROTEIN C

PUBN-DATE: December 21, 1995

INT-CL (IPC): C12N 15/13; C07K 16/40; C07K 16/46; C07K 17/00; A61K 39/395; A61K 33/06; A61K 38/19

EUR-CL (EPC): C07K016/40

APPL-NO: US09507372
APPL-DATE: June 9, 1995

PRIORITY-DATA:

IN: REZAIE, ALIREZA, ESMON, CHARLES T

AB: A Ca<2+> dependent recombinant antibody that specifically binds to a specific
twelve peptide sequence (E D Q V D P R L I D G K) in the activation region of the Protein C
has been constructed. The antibody does not bind to Activated Protein C and can be used to
inhibit activation of Protein C by thrombin-thrombomodulin, in purification of Protein C,
and in treatment of tumors.

L7: Entry 19 of 44
File: EPAB
Dec 21, 1995

DOCUMENT-IDENTIFIER: WO 9534652 A1
TITLE: CALCIUM BINDING RECOMBINANT ANTIBODY AGAINST PROTEIN C

FPAR:
A Ca<2+> dependent recombinant antibody that specifically binds to a specific twelve peptide
sequence (E D Q V D P R L I D G K) in the activation region of the Protein C has been
constructed. The antibody does not bind to Activated Protein C and can be used to inhibit
activation of Protein C by thrombin-thrombomodulin, in purification of Protein C, and in
treatment of tumors.

20. Document ID: US 5254532 A

L7: Entry 20 of 44
File: EPAB
Oct 19, 1993

PUB-NO: US005254532A
DOCUMENT-IDENTIFIER: US 5254532 A
TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use
of such a preparation and a method of producing the same

PUBN-DATE: October 19, 1993

INT-CL (IPC): A61K 37/00
EUR-CL (EPC): C07K014/745; C07K016/36, C07K016/40 , C12N009/64

APPL-NO: US84071992
APPL-DATE: February 21, 1992

PRIORITY-DATA:

IN: SCHWARZ, HANS P, MOLINARI, EWALD, LINNAU, YENDRA, PFEILER, SUSANNE

AB: A preparation for the treatment and prevention of thromboses and thromboembolic
complications is disclosed, which preparation has a content of protein S at a concentration
at least 50 times that present in native plasma and is free from C4b-binding protein,
optionally in combination with a content of activated protein C.

L7: Entry 20 of 44
File: EPAB
Oct 19, 1993

DOCUMENT-IDENTIFIER: US 5254532 A
TITLE: Preparation for treating and preventing thromboses and thromboembolic complications, use
of such a preparation and a method of producing the same

FPAR:
A preparation for the treatment and prevention of thromboses and thromboembolic complications is
disclosed, which preparation has a content of protein S at a concentration at least 50 times that
present in native plasma and is free from C4b-binding protein, optionally in combination with a
content of activated protein C.

21. Document ID: US 5143901 A

L7: Entry 21 of 44
File: EPAB
Sep 1, 1992

PUB-NO: US005143901A
DOCUMENT-IDENTIFIER: US 5143901 A
TITLE: TITLE DATA NOT AVAILABLE

PUBN-DATE: September 1, 1992

INT-CL (IPC): A61K 37/00
EUR-CL (EPC): C07K014/745; C07K016/36, C07K016/40 , C12N009/64

APPL-NO: US54035790
APPL-DATE: June 19, 1990

PRIORITY-DATA:

IN: SCHWARZ, HANS P, MOLINARI, EWALD, LINNAU, YENDRA, PFEILER, SUSANNE

AB: A preparation for the treatment and prevention of thromboses and thromboembolic
complications is disclosed, which preparation has a content of protein S at a concentration
at least 50 times that present in native plasma and is free from C4b-binding protein,
optionally in combination with a content of activated protein C.

L7: Entry 21 of 44
File: EPAB
Sep 1, 1992

DOCUMENT-IDENTIFIER: US 5143901 A
TITLE: TITLE DATA NOT AVAILABLE

FPAR:
A preparation for the treatment and prevention of thromboses and thromboembolic complications is disclosed, which preparation has a content of protein S at a concentration at least 50 times that present in native plasma and is free from C4b-binding protein, optionally in combination with a content of activated protein C.

22. Document ID: US 4638050 A

L7: Entry 22 of 44
File: EPAB
Jan 20, 1987

PUB-NO: US004638050A
DOCUMENT-IDENTIFIER: US 4638050 A
TITLE: Thrombin-binding substance and process for its production

PUBN-DATE: January 20, 1987

INT-CL (IPC): C07K 14/745
EUR-CL (EPC): C07K014/745

APPL-NO: US71382185
APPL-DATE: March 20, 1985

PRIORITY-DATA:

IN: AOKI, NOBUO, KUROSAWA, SHINICHIRO

AB: A thrombin-binding substance derived from human tissue and having the characteristics of (a) molecular weight: 88,000+/-20,000 in reduced condition and 71,000+/-20,000 in unreduced condition; (b) isoelectric point: pH 4.2+/-0.5; (c) affinity: strong for thrombin; (d) activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging clotting time; and (e) stability: stable over a pH range of 2 to 10 and stable to denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively useful for thrombolysis and anticoagulation.

L7: Entry 22 of 44
File: EPAB
Jan 20, 1987

DOCUMENT-IDENTIFIER: US 4638050 A
TITLE: Thrombin-binding substance and process for its production

FPAR:
A thrombin-binding substance derived from human tissue and having the characteristics of (a) molecular weight: 88,000+/-20,000 in reduced condition and 71,000+/-20,000 in unreduced condition; (b) isoelectric point: pH 4.2+/-0.5; (c) affinity: strong for thrombin; (d) activities: capable of promoting the thrombin-catalyzed activation of protein C and prolonging clotting time; and (e) stability: stable over a pH range of 2 to 10 and stable to denaturing agents (sodium dodecylsulfate and urea) and to a pepsin treatment, is effectively useful for thrombolysis and anticoagulation.

23. Document ID: WO 200066754 A1
L7: Entry 23 of 44
File: DWPI
Nov 9, 2000

DERWENT-ACC-NO: 2001-007227
DERWENT-WEEK: 200101

TITLE: Protein C derivatives, useful for treating vascular occlusive disorder, hypercoagulable state, thrombotic disorder and disease states predisposing thrombosis, comprises specific amino acid substitutions

PRIORITY-DATA: 1999US-0131801 (April 30, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200066754 A1	November 9, 2000	E	057	C12N015/57

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 200066754A1	April 13, 2000	2000WO-US08722	N/A

INT-CL (IPC): A61K 38/48; C12N 5/10; C12N 9/64; C12N 15/57

IN: GERLITZ, B E, JONES, B E

AB: NOVELTY - A protein C derivative (I) comprising a fully defined sequence of 419 amino acids or corresponding to a fully defined sequence of 461 amino acids, where amino acid at position 194, 195, 228, 249, 254, 302 or 316 is substituted by S, A, T, H, K, R, N, D, E, G or Q, such that amino acid at position 195 is not substituted with A and amino acid at position 254 is not substituted with T, is new., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following:, (1) a recombinant DNA molecule (II) encoding a protein C derivative in which L at position 194 is replaced with S or A and T at position 254 is replaced with S, and comprising a fully defined sequence of 1386 nucleotides;, (2) a pharmaceutical composition (PC) comprising a protein C derivative with increased resistance to serpins selected from L194S, L194S:T254S, or L194A:T254S;, (3) a vector (III) comprising (II);, (4) a host cell (IV) transformed with (III);, (5) an isolated nucleic

acid comprising
a protein C polynucleotide encoding at least 90% of amino acids of a fully defined sequence
(S1) comprising 419 amino acids;, (6) a protein C derivative comprising at least 90% of
amino acids of S1;, (7) an article of manufacture for human pharmaceutical use, comprising a
packaging material, and a vial comprising lyophilized (I);, (8) preparing (I); and, (9)
treating thrombotic and vascular occlusive disorders or, hypercoagulable states by
inhibiting binding of activated protein C polypeptides to inhibitor recognition sequences of
serpins, PCI and alpha -1-AT., ACTIVITY - Antibacterial; immunosuppressive; anticoagulant;
hemostatic; dermatological; tranquilizer; vulnerary; antiinflammatory; thrombolytic;
antisickling; antianemic; antiviral; cardiant; antianginal; cerebroprotective., MECHANISM OF
ACTION - Regulator of homeostasis by inactivating factors Va, and VIIIa in the coagulation
cascade; amidolytic., Amidolytic activity of recombinant human aPC polypeptides were
determined by hydrolysis of the tri-peptide chromogenic substrate S-2366
(Glu-Pro-Arg-p-nitroanilide). The anticoagulant activity was shown as measured clotting time
in an aPTT in 500 ng ml aPC. Reactions were performed in a 96-well micro l plate, and
amidolytic activity was measured as a change in absorbance units/minute at 405 nm.
Anti-coagulant activity was assessed by measuring the prolongation of clotting time in the
activated partial thromboplastin time clotting assay. Reactions were monitored in a
ThermoMax kinetic microtiter plate reader. The result for anticoagulant activity was found
to be 36 seconds for control, 114 seconds for wild-type aPC, and 108 seconds for L194S aPC.
Amidolytic activity was found to be N/A mM/second for control, 98 mM/second for wild-type
aPC, and 84 mM/second for L194S aPC., USE - (I) is useful for treating vascular occlusive
disorders, hypercoagulable states such as sepsis, disseminated intravascular coagulation,
purpura fulminans, major trauma, major surgery, burns, adult respiratory distress syndrome,
transplantation, deep vein thrombosis, heparin-induced thrombocytopenia, sickle cell
disease, thalassemia, viral hemorrhagic fever, thrombotic thrombocytopenic purpura, and
hemolytic uremic syndrome, and also useful for treating thrombotic disorders and acute
coronary syndromes such as myocardial infarction, unstable angina, and stroke., ADVANTAGE -
Protein C derivatives with amino acid substitutions result in increased resistance to
inactivation by serpins when compared to wild-type activated human protein C. They also have
longer half-lives in human blood and hence require either less frequent administration
and/or smaller dosage than wild type human protein C for treating disorders.

L7: Entry 23 of 44

File: DWPI

Nov 9, 2000

DERWENT-ACC-NO: 2001-007227
DERWENT-WEEK: 200101
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TITLE: Protein C derivatives, useful for treating vascular occlusive disorder, hypercoagulable
state, thrombotic disorder and disease states predisposing thrombosis, comprises specific amino
acid substitutions

ABTX:
(9) treating thrombotic and vascular occlusive disorders or, hypercoagulable states by inhibiting
binding of activated protein C polypeptides to inhibitor recognition sequences of serpins, PCI
and alpha -1-AT.

24. Document ID: WO 200062068 A1
L7: Entry 24 of 44

File: DWPI

Oct 19, 2000

DERWENT-ACC-NO: 2000-679516
DERWENT-WEEK: 200066
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TITLE: Typing, diagnoses, prevention and/or treatment of prion disease e.g. spongiform
encephalopathies using binding of metal ions to PrP(SC)

PRIORITY-DATA: 1999GB-0008059 (April 9, 1999)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 200062068 A1	October 19, 2000	E	049	G01N033/569

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 200062068A1	April 7, 2000	2000WO-GB01327	N/A

INT-CL (IPC): C07K 14/47; G01N 33/569; G01N 33/68

IN: COLLINGE, J, WADSWORTH, J D F

AB: NOVELTY - Typing PrPsc comprises (a) treating a sample containing a PrPsc protein
to remove one or more bound metal ions from PrPsc; (b) digesting PrPsc protein; and (c)
comparing the products of the digestion with the products of a control method in which the
sample is not treated to remove bound metal ions, any difference being indicative of the
presence of type 1 or type 2 PrPsc and no difference being indicative of type 3 or type 4
PrPsc., DETAILED DESCRIPTION - INDEPENDENT CLAIMS are also included for the following: (i) a
method of altering the conformation of PrPsc comprising treating PrPsc with an agent which
affects the binding of PrPsc to one or more divalent metal ions; (ii) use of an agent
capable of affecting the binding of PrPsc to one or more divalent metal ions in the
manufacture of a composition for use in the prevention, treatment and/or diagnosis of a
prion disease; (iii) a method for screening for an agent capable of altering

the
conformation of type 1 and/or type 2 PrPsc comprising (a) exposing type 1 and/or type 2
PrPsc to the agent; (b) digesting the PrPsc; (c) comparing the digestion products with
products produced under the same conditions in the absence of the agent, a difference being
indicative of a change in the conformation of type 1 and/or type 2 PrPsc; (iv) a method for
screening for an agent for use in the diagnosis, prevention and/or treatment of a prion
disease comprising testing an agent for its ability to convert type 1 PrPsc to type 2 PrPsc
or type 2- PrPsc or vice versa and/or type 2 PrPsc to type 2- PrPsc or vice versa; (v)
isolated PrPsc type 2- which when digested produces the same digestion products as type 1
and/or type 2 PrPsc which have been treated prior to digestion to remove one or more bound
metal ions; and (vi) use of isolated PrPsc type 2- in the manufacture of a medicament for
use in the manufacture of a composition for use in the diagnosis, prevention and/or
treatment of a prion disease., ACTIVITY - Neuroprotective., MECHANISM OF ACTION - None
given., USE - For typing, diagnoses, prevention and/or treatment of prion disease e.g.
spongiform encephalopathies such as Creutzfeldt-Jakob disease and bovine spongiform
encephalopathy.

L7: Entry 24 of 44
File: DWPI
Oct 19, 2000

DERWENT-ACC-NO: 2000-679516
DERWENT-WEEK: 200066

TITLE: Typing, diagnoses, prevention and/or treatment of prion disease e.g. spongiform
encephalopathies using binding of metal ions to PrP(SC)

ABTX:
NOVELTY - Typing PrPsc comprises (a) treating a sample containing a PrPsc protein to remove one
or more bound metal ions from PrPsc; (b) digesting PrPsc protein; and (c) comparing the products
of the digestion with the products of a control method in which the sample is not treated to
remove bound metal ions, any difference being indicative of the presence of type 1 or type 2
PrPsc and no difference being indicative of type 3 or type 4 PrPsc.

25. Document ID: AU 9959013 A, WO 200010609 A1
L7: Entry 25 of 44
File: DWPI
Mar 14, 2000

DERWENT-ACC-NO: 2000-224557
DERWENT-WEEK: 200031

TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful for treatment or
diagnosis of cardiovascular disease, by targeting the endothelial cell protein C receptor

PRIORITY-DATA: 1998US-0139425 (August 25, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 9959013 A	March 14, 2000	N/A	000	A61K045/06
WO 200010609 A1	March 2, 2000	E	023	A61K045/06

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 9959013A	August 25, 1999	1999AU-0059013	N/A
AU 9959013A		WO 200010609	Based on
WO 200010609A1	August 25, 1999	1999WO-US19480	N/A

INT-CL (IPC): A61K 45/06

IN: ESMON, C T, XU, J

AB: NOVELTY - A method of selectively delivering molecules (I) to the nucleus of
endothelial cells of large vessels by administering a conjugate (C) of (I) with an agent
(II) that binds selectively to endothelial protein C receptor (EPCR)., DETAILED DESCRIPTION
- An INDEPENDENT CLAIM is also included for a conjugate of (I) which is not a diagnostic
label, with either protein C, optionally activated, or an antibody reactive with EPCR, or
fragments of it which bind EPCR., ACTIVITY - Antithrombotic; fibrinolytic; antiinflammatory;
anticoagulant; vasoconstrictor., MECHANISM OF ACTION - EPCR translocates from the plasma
membrane to the nucleus, and transports molecules that bind to it., USE - (C) are used to
deliver therapeutic agents, e.g. nucleic acids, proteins, expression inhibitors,
anti-inflammatories, anticoagulants, growth hormones etc., or diagnostic agents such as
radiolabels, fluorescent labels and enzymatic labels, particularly in the cases of
cardiovascular disease. Typical applications include preventing thrombosis, increasing
fibrinolytic activity, or inhibiting leukocyte adhesion., ADVANTAGE - Since EPCR is present
mainly on endothelial cells of large vessels, rather than similar cells in capillaries or
other small vessels, especially in arteries, using it as target provides selective delivery
of (I) with reduced risks of systemic complications. Serum stimulates nuclear translocation
of EPCR, so delivery is enhanced during inflammatory or coagulative processes, often present
in the treated subjects.

L7: Entry 25 of 44

File: DWPI

Mar 14, 2000

DERWENT-ACC-NO: 2000-224557
DERWENT-WEEK: 200031

TITLE: Specific delivery to nuclei of large vessel endothelial cells, useful for treatment or
diagnosis of cardiovascular disease, by targeting the endothelial cell protein C receptor

ABTX:
DETAILED DESCRIPTION - An INDEPENDENT CLAIM is also included for a conjugate of (I) which is not
a diagnostic label, with either protein C, optionally activated, or an antibody reactive with
EPCR, or fragments of it which bind EPCR.

26. Document ID: EP 994946 A1, WO 9909164 A1, AU 9892928 A
L7: Entry 26 of 44

File: DWPI

Apr 26, 2000

DERWENT-ACC-NO: 1999-190163
DERWENT-WEEK: 200025

TITLE: New coding sequence haplotypes of the human BRCA2 gene - used to develop products for
determining susceptibility to, detection and treatment of breast or ovarian cancer

PRIORITY-DATA: 1998US-0084471 (May 22, 1998), 1997US-0055784 (August 15, 1997), 1997US-0064926
(November 7, 1997), 1997US-0065367 (November 12, 1997), 1998US-0071715 (May 1, 1998)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 994946 A1	April 26, 2000	E	000	C12N015/12
WO 9909164 A1	February 25, 1999	E	215	C12N015/12
AU 9892928 A	March 8, 1999	N/A	000	C12N015/12

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 994946A1	August 14, 1998	1998EP-0945756	N/A
EP 994946A1	August 14, 1998	1998WO-US16905	N/A
EP 994946A1		WO 9909164	Based on
WO 9909164A1	August 14, 1998	1998WO-US16905	N/A
AU 9892928A	August 14, 1998	1998AU-0092928	N/A
AU 9892928A		WO 9909164	Based on

INT-CL (IPC): A61K 38/17; A61K 48/00; C07K 14/47; C07K 16/18; C12N 15/12; C12Q 1/68

IN: ESKANDARI, T, JACKSON, G M, MURPHY, P D, OLSON, S J, PARK, M, RABIN, M B,
SCHRYER, B, WHITE, M B, YOSHIKAWA, M

AB: NOVELTY - Coding sequence haplotypes of the human BRAC2 gene are new., DETAILED
DESCRIPTION - New genomic DNA contains a BRCA2 gene where the first 12 nucleotides (it)
beginning exon 5 are 5'-TCCTGTTGTTCT-3' as in sequence (I) (TCCTGTTGTT CTACAATGTA CACATGTAAC
ACCACAAAGA GATAAGTCAG), where nt numbers 5782-5790 are GTTTGTGTT as in sequence (IV) of
10485 nt, and where the last 20 nt encoding exon 15 are 5'-CTGCGTGTTCTCATAAACAG-3' as in
sequence (II) of 182 nt and the first 20 nt beginning at exon 16 are
5'-CTGTATACGTATGGCGTTTC-3' as in sequence (III) of 188 nt., INDEPENDENT CLAIMS are also
included for: (1) a DNA comprising a BRCA2 coding sequence, where nt numbers 643-666 are
CTTAGTGAAAGTCCTGTTGTTCTA and where nt numbers 5782-5790 are GTTTGTGTT; (2) a BRCA2 protein
having the following amino acids (aa) at the following peptide numbers: 289 asparagine, 372
histidine, 894 valine, 991 asparagine, 1852 valine, 1853 cystein, 1854 valine, 2951 alanine
as in sequence (V) of 3418 aa; (3) a BRCA2 protein having the following aa at the following
peptide numbers: 289 asparagine, 372 asparagine, 599 serine, 894 valine, 991 asparagine,
2951 alanine; (4) a BRCA2 protein having the following aa at the following peptide numbers:
289 histidine, 372 histidine, 894 valine, 991 aspartic acid, 2951 alanine as in sequence
(IX) of 3418 aa; (5) a BRCA2 protein having the following aa at the following peptide
numbers: 289 histidine, 372 asparagine, 894 isoleucine, 991 aspartic acid, 2951 threonine as
in sequence (XIII) of 3418 aa; (6) a haplotype of BRCA2 coding sequence (BRCA2(omi1) as in
(IV) or a complementary sequence; (7) a BRCA2 protein comprising an aa sequence derived from
BRCA2 (omi) as in (V); (8) a haplotype of BRCA2 coding sequence BRCA2(omi2) as in (VI) or a
complementary sequence; (9) a BRCA2 protein comprising an aa sequence derived from
BRCA2(omi2) as in (VII); (10) a haplotype of BRCA2 coding sequence (BRCA2(omi3) as (VIII) or
a complementary sequence; (11) a BRCA2 protein comprising an aa sequence derived from
BRCA2(omi3) as in (IX); (12) a haplotype of BRCA2 coding sequence (BRCA2(omi4)) as in (X) or
a complementary sequence; (13) a BRCA2 protein comprising an aa sequence derived from
BRCA2(omi4) as in (XI); (14) a haplotype of BRCA2 coding sequence BRCA2(omi5) as in (XII) or

a complementary sequence; (15) a BRCA2 protein comprising an aa sequence derived from
BRCA2(omi5) as in (XIII); (16) an ON primer capable of hybridising to a sample of BRCA2 gene
or its respective complementary sequences selected from sequences given in the specifcation;
(17) a chip array having n elements for perfonning allele specific sequence-based techniques
comprising a solid phase chip and oligonucleotides (ONs) having n different nt sequences
(NSs), where n at least 10, where the ONs are bound to the solid phase chip in a manner
which permits the ONs to hybridise to complementary ONs or polynucleotides (PNs), where ONs
having different NS are bound to the solid phase chip at different locations so that a
particular location on the solid phase chip exclusively binds ONs having a specific NS, and
where at least 10 ONs are capable of specifically hybridising to the BRCA2 DNA having a
sequence as in sequence (IV), (VI), (VIII), (X), (XII) or their respective complementary
sequences, at least one ON being capable of specifically hybridising at each of the nt
positions 1093, 1342, 1593, 2457, 2908, 3199, 3624, 4035, 7470, 9079 or complements; (18) a
method of performing gene therapy on a patient comprising: (a) contacting cancer cells in
vivo with a vector comprising DNA containing at least a portion of BRCA2 sequence selected
from sequence (IV), (VI), (VIII), (X), (XII) or the respective complementary sequences; (b)
allowing the vector to enter the cancer cells; and (c) measuring a reduction in tumour
growth; (19) a method of performing gene therapy on a patient or a sample comprising: (a)
contacting cells in vivo or in vitro with a vector comprising DNA containing at least a
portion of BRCA2 sequence selected from sequence (IV), (VI), (VIII), (X), (XII) or the
respective complementary sequences; and (b) allowing the vector to enter the cells; where
the patient has a reduced susceptibility for developing a cancer associated with a mutation
in the BRCA2 gene; (20) a method of treating a patient suspected of having a tumour
comprising: (a) administering to a patient a BRCA2 tumor growth inhibitor having an aa
sequence selected from sequence (V), (VII), (IX), (XI), (XIII) or fragments or functional
equivalents; (b) allowing the patients cells to take up the protein; and (c) measuring a
reduction in tumor growth; (21) a method of preventing the formation or growth of a tumor
comprising: (a) administering to a patient a BRCA2 tumour growth inhibiting protein having
an aa sequence selected from sequences (V), (VII), (IX), (XI), (XIII) or fragments or
functional equivalents; and (b) allowing the patient cells to take up the protein; (22) a
cloning vector comprising: (a) a DNA sequence (IV), (VI), (VIII), (X), (XII) or any
fragment; and (b) one or more suitable regulatory sequences to induce replication and/or
integration in a host cell; (23) an expression vector comprising a DNA sequence as in
sequences (IV), (VI), (VIII), (X), (XII) or any fragments operatively linked to one or more
promoter sequences capable of directing expression of the sequence in a host cell; (24) a
host cell transformed with a vector as in (22) or (23); (25) a BRCA2 polypeptide which is
selected from: (a) a fragment of BRCA2 protein sequence as in sequence (V), (VII), (IX),
(XI), or (XIII); (b) an aa sequence which is homologous to the BRCA2 protein sequence as in
(V), (VII), (IX), (XI), or (XIII); (c) a molecule which has similar function to the BRCA2
protein; and (d) a fusion protein of (a), (b) or (c); and (26) a diagnostic reagent
comprising a molecule selected from: (a) a DNA sequence as in (23); (b) a nucleic acid
fragment of (a) comprising at least 10 nt; (c) a sequence which hybridises to (a) or (b);
(d) a polypeptide as in (2)-(5), (7), (9), (13), (15), or (25) in a carrier., USE - The
products and methods can be used for identifying mutations in the BRCA2 gene leading to
predisposition or higher susceptibility to breast or ovarian cancer. They can also be used
for detection and gene therapy for breast and ovarian cancers, They can be used in methods
for monitoring disease progression, for determining patients suited for gene and protein
replacement progression, or for detecting the presence or quantifying the amount of a tumour
growth inhibitor following such therapy. The BRCA2 protein, polypeptides, their functional
equivalents, antibodies, and PNs may also be useful in the study of the characteristics of
BRCA2 proteins, such as structure and function of BRCA2 in oncogenesis or subcellular
localisation of BRCA2 protein in normal and cancerous cells.

L7: Entry 26 of 44

File: DWPI

Apr 26, 2000

DERWENT-ACC-NO: 1999-190163
DERWENT-WEEK: 200025

TITLE: New coding sequence haplotypes of the human BRCA2 gene - used to develop products for
determining susceptibility to, detection and treatment of breast or ovarian cancer

ABTX:
INDEPENDENT CLAIMS are also included for: (1) a DNA comprising a BRCA2 coding sequence, where nt
numbers 643-666 are CTTAGTGAAAGTCCTGTTGTTCTA and where nt numbers 5782-5790 are GTTTGTGTT; (2) a
BRCA2 protein having the following amino acids (aa) at the following peptide numbers: 289
asparagine, 372 histidine, 894 valine, 991 asparagine, 1852 valine, 1853 cystein, 1854 valine,
2951 alanine as in sequence (V) of 3418 aa; (3) a BRCA2 protein having the following aa at the
following peptide numbers: 289 asparagine, 372 asparagine, 599 serine, 894 valine, 991
asparagine, 2951 alanine; (4) a BRCA2 protein having the following aa at the following peptide
numbers: 289 histidine, 372 histidine, 894 valine, 991 aspartic acid, 2951 alanine as in sequence
(IX) of 3418 aa; (5) a BRCA2 protein having the following aa at the following peptide numbers:
289 histidine, 372 asparagine, 894 isoleucine, 991 aspartic acid, 2951 threonine as in sequence
(XIII) of 3418 aa; (6) a haplotype of BRCA2 coding sequence (BRCA2(omi1) as in (IV) or a
complementary sequence; (7) a BRCA2 protein comprising an aa sequence derived from BRCA2 (omi) as
in (V); (8) a haplotype of BRCA2 coding sequence BRCA2(omi2) as in (VI) or a complementary
sequence; (9) a BRCA2 protein comprising an aa sequence derived from BRCA2(omi2) as in (VII);
(10) a haplotype of BRCA2 coding sequence (BRCA2(omi3) as (VIII) or a complementary sequence;
(11) a BRCA2 protein comprising an aa sequence derived from BRCA2(omi3) as in (IX); (12) a
haplotype of BRCA2 coding sequence (BRCA2(omi4)) as in (X) or a complementary sequence; (13) a
BRCA2 protein comprising an aa sequence derived from BRCA2(omi4) as in (XI); (14) a haplotype of

BRCA2 coding sequence BRCA2(omi5) as in (XII) or a complementary sequence; (15) a BRCA2 protein
comprising an aa sequence derived from BRCA2(omi5) as in (XIII); (16) an ON primer capable of
hybridising to a sample of BRCA2 gene or its respective complementary sequences selected from
sequences given in the specifcation; (17) a chip array having n elements for performing allele
specific sequence-based techniques comprising a solid phase chip and oligonucleotides (ONs)
having n different nt sequences (NSs), where n at least 10, where the ONs are bound to the solid
phase chip in a manner which permits the ONs to hybridise to complementary ONs or polynucleotides
(PNs), where ONs having different NS are bound to the solid phase chip at different locations so
that a particular location on the solid phase chip exclusively binds ONs having a specific NS,
and where at least 10 ONs are capable of specifically hybridising to the BRCA2 DNA having a
sequence as in sequence (IV), (VI), (VIII), (X), (XII) or their respective complementary
sequences, at least one ON being capable of specifically hybridising at each of the nt positions
1093, 1342, 1593, 2457, 2908, 3199, 3624, 4035, 7470, 9079 or complements; (18) a method of
performing gene therapy on a patient comprising: (a) contacting cancer cells in vivo with a
vector comprising DNA containing at least a portion of BRCA2 sequence selected from sequence
(IV), (VI), (VIII), (X), (XII) or the respective complementary sequences; (b) allowing the vector
to enter the cancer cells; and (c) measuring a reduction in tumour growth; (19) a method of
performing gene therapy on a patient or a sample comprising: (a) contacting cells in vivo or in
vitro with a vector comprising DNA containing at least a portion of BRCA2 sequence selected from
sequence (IV), (VI), (VIII), (X), (XII) or the respective complementary sequences; and (b)
allowing the vector to enter the cells; where the patient has a reduced susceptibility for
developing a cancer associated with a mutation in the BRCA2 gene; (20) a method of treating a
patient suspected of having a tumour comprising: (a) administering to a patient a BRCA2 tumor
growth inhibitor having an aa sequence selected from sequence (V), (VII), (IX), (XI), (XIII) or
fragments or functional equivalents; (b) allowing the patients cells to take up the protein; and
(c) measuring a reduction in tumor growth; (21) a method of preventing the formation or growth of
a tumor comprising: (a) administering to a patient a BRCA2 tumour growth inhibiting protein
having an aa sequence selected from sequences (V), (VII), (IX), (XI), (XIII) or fragments or
functional equivalents; and (b) allowing the patient cells to take up the protein; (22) a cloning
vector comprising: (a) a DNA sequence (IV), (VI), (VIII), (X), (XII) or any fragment; and (b) one
or more suitable regulatory sequences to induce replication and/or integration in a host cell;
(23) an expression vector comprising a DNA sequence as in sequences (IV), (VI), (VIII), (X),
(XII) or any fragments operatively linked to one or more promoter sequences capable of directing
expression of the sequence in a host cell; (24) a host cell transformed with a vector as in (22)
or (23); (25) a BRCA2 polypeptide which is selected from: (a) a fragment of BRCA2 protein
sequence as in sequence (V), (VII), (IX), (XI), or (XIII); (b) an aa sequence which is homologous
to the BRCA2 protein sequence as in (V), (VII), (IX), (XI), or (XIII); (c) a molecule which has
similar function to the BRCA2 protein; and (d) a fusion protein of (a), (b) or (c); and (26) a
diagnostic reagent comprising a molecule selected from: (a) a DNA sequence as in (23); (b) a
nucleic acid fragment of (a) comprising at least 10 nt; (c) a sequence which hybridises to (a) or
(b); (d) a polypeptide as in (2)-(5), (7), (9), (13), (15), or (25) in a carrier.

27. Document ID: EP 1003783 A2, WO 9907736 A2, FR 2767135 A1, FR 2767136 A1, AU 9885563 A
L7: Entry 27 of 44

File: DWPI

May 31, 2000

DERWENT-ACC-NO: 1999-167364
DERWENT-WEEK: 200031

TITLE: Use of lipolysis stimulated receptor - for developing agents for modulating partitioning
of dietary lipids between the liver and peripheral tissues, e.g. for treating obesity

PRIORITY-DATA: 1998FR-0005032 (April 22, 1998), 1997FR-0010088 (August 6, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 1003783 A2	May 31, 2000	E	000	C07K014/715
WO 9907736 A2	February 18, 1999	E	076	C07K014/00
FR 2767135 A1	February 12, 1999	N/A	000	C07K014/705
FR 2767136 A1	February 12, 1999	N/A	000	C07K014/715
AU 9885563 A	March 1, 1999	N/A	000	C07K014/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 1003783A2	August 6, 1998	1998EP-0936610	N/A
EP 1003783A2	August 6, 1998	1998WO-IB01256	N/A
EP 1003783A2		WO 9907736	Based on

WO 9907736A2
August 6, 1998
1998WO-IB01256
N/A
FR 2767135A1
April 22, 1998
1998FR-0005032
N/A
FR 2767136A1
August 6, 1997
1997FR-0010088
N/A
AU 9885563A
August 6, 1998
1998AU-0085563
N/A
AU 9885563A
WO 9907736
Based on

INT-CL (IPC): A01K 67/027; A61K 38/17; A61K 38/19; A61K 39/395; A61K 48/00; C07K 14/00; C07K 14/47; C07K 14/705; C07K 14/715; C07K 16/28; C12N 5/10; C12N 15/12; C12N 15/85; C12Q 1/68; G01N 33/68

IN: BIHAIN, B, BOUGUELERET, L, YEN-POTIN, F, YEN, P F

AB: NOVELTY - Agents which influence the partitioning of dietary lipids between the liver and peripheral tissues for use as medicaments. 7 polypeptide sequences (the sequences relate to complement C1qA, complement C1qB, complement C1qC, multimerin, cerebellin, ApM1, AdipoQ and acrp30) and two consensus sequences are given in the specification and are potentially useful as these agents., DETAILED DESCRIPTION - An agent is claimed which influences the partitioning of dietary lipids between the liver and peripheral tissues for use as a medicament., INDEPENDENT CLAIMS are included for: (1) a polypeptide comprising a consensus sequence selected from sequence (I): PheX(5) [AsnAsp]X(4) [PheTyrTrpLeu]X(6) PheX(5)GlyXTyrXPhe X[PheTyr] and (II): [SerThr]XPhe[SerThr] Gly[PheTyr]Leu[LeuVal] [PheTyr] for use as a medicament; (2) a polypeptide comprising an amino acid sequence selected from polypeptides having at least 25%, 50% or 80% homology to one of the sequences (VII)-(XIV) given in the specification, for use as a medicament; (3) a C1q polypeptide, derivative, homologue or a fragment of any of the preceding compounds for use as a medicament; (4) an AdipoQ polypeptide or a derivative, homologue or fragment for use as a medicament; (5) an ApM1 polypeptide, derivative, homologue or fragment for use as a medicament; (6) a composition for modulating the activity of LSR comprising a compound having binding specificity for the gC1q.R protein, where the compound is not a subunit of the LSR; and a carrier; (7) a method of reducing plasma lipoprotein levels in an animal comprising: (a) identifying an animal having a measurable plasma lipoprotein level; (b) administering to the animal a composition that includes a carrier and a polypeptide that is at least 25% homologous to an ApM1 protein; and (c) allowing passage of a period of time to permit reduction in the measurable plasma lipoprotein level; (8) a method for treating an animal having a condition in which it is desirable to increase the partitioning of dietary lipids to the liver, comprising administering an LSR agonist to the animal having the condition; (9) a method for treating an animal having a condition in which it is desirable to decrease the partitioning of dietary lipids to the liver, comprising administering an LSR antagonist to the animal having the condition; (10) an agent which increases the activity of a compound which increases the partitioning of dietary lipids to the liver for use as a pharmaceutical; (11) an agent which decreases the activity of a compound which increases the partitioning of dietary lipids to the liver for use as a pharmaceutical; (12) a method for decreasing the partitioning of dietary lipids to the liver comprising administering an agent which decreases the activity of a compound selected from adipoQ, ApM1, C1q, compounds comprising at least one sequence selected from sequences (I) and (II), compounds comprising an amino acid sequence having at least 25% homology to a sequence selected from sequences (VII)-(XIV) given in the specification, (129, 130, 124, 130, 130, 130, 130, and 126 amino acids respectively), polypeptides comprising an amino acid sequence having at least 50% homology to a sequence selected from sequences (VII)-(XIV), and polypeptides comprising an amino acid sequence having at least 80% homology to a sequence selected from sequences (VII)-(XIV)., USE - Compounds that influences the partitioning of dietary lipids between the liver and peripheral tissues can be used in medicament for treating a condition in which the partitioning of dietary lipids to the liver is abnormal (claimed). A polypeptide having binding specificity for a gamma subunit of the lipolysis stimulated receptor (LSR) or a gC1q.R or a gC1q.R homologue can be used for treatment of obesity, where the polypeptide is not a subunit of the LSR (claimed). The agents which increase partitioning of dietary lipids to the liver can be used for treating obesity-related atherosclerosis, obesity-related insulin resistance, obesity-related hypertension, micoangiopathic lesions resulting from obesity-related Type II diabetes, ocular lesions caused by microangiopathy in obese individuals with Type II diabetes, and renal lesions caused by microangiopathy in obese individuals with Type II diabetes (claimed). Agents which decrease the partitioning of dietary lipids to the liver can be used for treating cachexia in subjects with, neoplastic or para-neoplastic syndrome or eating disorders (claimed)., Studies showed that gC1q-R has a sequence analogous to LSR. Incubation of rat hepatocytes with C1q led to activation of Lipolysis stimulated receptor (LSR). The effect of C1q led to the investigation of proteins sharing structured homology to C1q. The murine proteins AdipoQ and the human ApM1 protein clearly exhibited marked homologies. Recombinant AdipoQ was shown to stimulate LSR activity in cultured rat hepatocytes. Agents which modify the structure of the LSR complex by perturbing interaction of the gamma subunit with the LSR activate the LSR in the absence of free fatty acids The effect of this perturbation can be measured as increased hepatocyte binding, internalisation and degradation of lipoproteins.

L7: Entry 27 of 44

File: DWPI

May 31, 2000

DERWENT-ACC-NO: 1999-167364
DERWENT-WEEK: 200031

TITLE: Use of lipolysis stimulated receptor - for developing agents for modulating partitioning
of dietary lipids between the liver and peripheral tissues, e.g. for treating obesity

ABTX:
INDEPEND ENT CLAIMS are included for: (1) a polypeptide comprising a consensus sequence selected
from sequence (I): PheX(5) [AsnAsp]X(4) [PheTyrTrpLeu]X(6) PheX(5)GlyXTyrXPhe X[PheTyr} and (II):
[SerThr]XPhe[SerThr] Gly[PheTyr]Leu[LeuVal] [PheTyr] for use as a medicament; (2) a polypeptide
comprising an amino acid sequence selected from polypeptides having at least 25%, 50% or 80%
homology to one of the sequences (VII)-(XIV) given in the specification, for use as a medicament;
(3) a C1q polypeptide, derivative, homologue or a fragment of any of the preceding compounds for
use as a medicament; (4) an AdipoQ polypeptide or a derivative, homologue or fragment for use as
a medicament; (5) an ApM1 polypeptide, derivative, homologue or fragment for use as a medicament;
(6) a composition for modulating the activity of LSR comprising a compound having binding
specificity for the gC1q.R protein, where the compound is not a subunit of the LSR; and a
carrier; (7) a method of reducing plasma lipoprotein levels in an animal comprising: (a)
identifying an animal having a measurable plasma lipoprotein level; (b) administering to the
animal a composition that includes a carrier and a polypeptide that is at least 25% homologous to
an ApM1 protein; and (c) allowing passage of a period of time to permit reduction in the
measurable plasma lipoprotein level; (8) a method for treating an animal having a condition in
which it is desirable to increase the partitioning of dietary lipids to the liver, comprising
administering an LSR agonist to the animal having the condition; (9) a method for treating an
animal having a condition in which it is desirable to decrease the partitioning of dietary lipids
to the liver, comprising administering an LSR antagonist to the animal having the condition; (10)
an agent which increases the activity of a compound which increases the partitioning of dietary
lipids to the liver for use as a pharmaceutical; (11) an agent which decreases the activity of a
compound which increases the partitioning of dietary lipids to the liver for use as a
pharmaceutical; (12) a method for decreasing the partitioning of dietary lipids to the liver
comprising administering an agent which decreases the activity of a compound selected from
adipoQ, ApM1, C1q, compounds comprising at least one sequence selected from sequences (I) and
(II), compounds comprising an amino acid sequence having at least 25% homology to a sequence
selected from sequences (VII)-(XIV) given in the specification, (129, 130, 124, 130, 130, 130,
130, and 126 amino acids respectively), polypeptides comprising an amino acid sequence having at
least 50% homology to a sequence selected from sequences (VII)-(XIV), and polypeptides comprising
an amino acid sequence having at least 80% homology to a sequence selected from sequences
(VII)-(XIV).

28. Document ID: US 5948639 A, WO 9845467 A1, AU 9869681 A
L7: Entry 28 of 44
File: DWPI
Sep 7, 1999

DERWENT-ACC-NO: 1998-583204
DERWENT-WEEK: 199943

TITLE: Nucleic acid encoding endothelial MAD interactor 1 - for modulating cell proliferation and
differentiation, e.g. in cases of atherosclerosis and cancer of colon or pancreas

PRIORITY-DATA: 1997US-0844312 (April 10, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5948639 A	September 7, 1999	N/A	000	C12P021/00
WO 9845467 A1	October 15, 1998	E	095	C12P021/00
AU 9869681 A	October 30, 1998	N/A	000	C12P021/00

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 5948639A	April 10, 1997	1997US-0844312	N/A
WO 9845467A1	April 10, 1998	1998WO-US07356	N/A
AU 9869681A	April 10, 1998	1998AU-0069681	N/A
AU 9869681A		WO 9845467	Based on

INT-CL (IPC): A61K 38/18; C07H 21/04; C07K 14/46; C12N 1/21; C12N 5/10; C12N 15/00; C12N 15/12; C12P 21/00

IN: FALB, D A, GIMENO, C J

AB: New isolated nucleic acid (I) encodes EMI1 (endothelial mothers against dpp (MAD)
(sic) interactor 1), or biologically active parts of it, or its homologues that are able to
modulate a TGF beta (transfomin g growth factor) response in TGF beta responsive cells.,
Also new are: (1) isolated nucleic acid (Ia) of at least 15 nucleotides (nt) that hybridise
to a 1290 bp sequence (1) reproduced, or to the DNA insert of ATCC 98375:, (2) isolated
nucleic acid (Ib) encoding an EMI1 fusion protein (II):, (3) nucleic acid (Ic) antisense to
(I):, (4) vectors containing (I):, (5) host cells containing such vectors:, (6) isolated
EMI1 protein (III), its fragments or homologues that can modulate a TGF beta response:, (7)

fusion protein (II);, (8) antigenic EMI1 peptides of at least 8 amino acids (aa) including
an epitope;, (9) antibodies (Ab) specific for EMI1;, (10) non-human transgenic animals
containing cells having an EMI1 gene or homologously recombinant animals containing cells
having an altered EMI1 gene;, (11) processes for identifying compounds that: (a) can be used
to treat disorders characterised by aberrant EMI1 expression or activity, (b) bind to EMI1
protein or (c) inhibit interaction of EMI1 with a target molecule., USE - MAD proteins have
been implicated in the transforming growth factor beta (TGF- beta) cell signalling
pathways. Cells as in (5) are used to produce recombinant EMI1, used to raise Ab (for use as
immunoassay or affinity purification reagents, also therapeutically); for drug screening
and to treat EMI1 deficiency. Compounds identified in (11) are used to modulate cell
activities (e.g. proliferation and differentiation), particularly in cells (endothelial or
epithelial) that respond to TGF beta through a signalling pathway that involves EMI1,
especially for treatment of cardiovascular disease (specifically atherosclerosis but also
ischaemia/reperfusion, hypertension, restenosis and arterial inflammation) or proliferative
diseases, especially cancer of gut-derived cells, e.g. colorectal or pancreatic cancer, also
to modulate angiogenesis, treat autoimmune disease or fibrosis and to regulate wound
healing. Primers and probes based on (I), and Ab, are used to detect EMI1 RNA, or protein,
in standard assays, also to identify and clone EMI1 homologues, while detection of changes
in the EMI1 g ene is used to assess risk of disease associated with aberrant EMI1 expression
or activity. The animals as in (10) are useful for drug screening., New isolated nucleic
acid (I) encodes EMI1 (endothelial mothers against dpp (MAD) (sic) interactor 1), or
biologically active parts of it, or its homologues that are able to modulate a TGF beta
(transformin g growth factor) response in TGF beta responsive cells., Also new are: (1)
isolated nucleic acid (Ia) of at least 15 nucleotides (nt) that hybridise to a 1290 bp
sequence (1) reproduced, or to the DNA insert of ATCC 98375;, (2) isolated nucleic acid (Ib)
encoding an EMI1 fusion protein (II);, (3) nucleic acid (Ic) antisense to (I);, (4) vectors
containing (I);, (5) host cells containing such vectors;, (6) isolated EMI1 protein (III),
its fragments or homologues that can modulate a TGF beta response;, (7) fusion protein
(II);, (8) antigenic EMI1 peptides of at least 8 amino acids (aa) including an epitope;, (9)
antibodies (Ab) specific for EMI1;, (10) non-human transgenic animals containing cells
having an EMI1 gene or homologously recombinant animals containing cells having an altered
EMI1 gene;, (11) processes for identifying compounds that: (a) can be used to treat
disorders characterised by aberrant EMI1 expression or activity, (b) bind to EMI1 protein or
(c) inhibit interaction of EMI1 with a target molecule., USE - MAD proteins have been
implicated in the transforming growth factor beta (TGF- beta) cell signalling pathways.
Cells as in (5) are used to produce recombinant EMI1, used to raise Ab (for use as
immunoassay or affinity purification reagents, also therapeutically); for drug screening
and to treat EMI1 deficiency. Compounds identified in (11) are used to modulate cell
activities (e.g. proliferation and differentiation), particularly in cells (endothelial or
epithelial) that respond to TGF beta through a signalling pathway that involves EMI1,
especially for treatment of cardiovascular disease (specifically atherosclerosis but also
ischaemia/reperfusion, hypertension, restenosis and arterial inflammation) or proliferative
diseases, especially cancer of gut-derived cells, e.g. colorectal or pancreatic cancer, also
to modulate angiogenesis, treat autoimmune disease or fibrosis and to regulate wound
healing. Primers and probes based on (I), and Ab, are used to detect EMI1 RNA, or protein,
in standard assays, also to identify and clone EMI1 homologues, while detection of changes
in the EMI1 g ene is used to assess risk of disease associated with aberrant EMI1 expression
or activity. The animals as in (10) are useful for drug screening.

L7: Entry 28 of 44

File: DWPI

Sep 7, 1999

DERWENT-ACC-NO: 1998-583204
DERWENT-WEEK: 199943

TITLE: Nucleic acid encoding endothelial MAD interactor I - for modulating cell proliferation and
differentiation, e.g. in cases of atherosclerosis and cancer of colon or pancreas

ABTX:
(11) processes for identifying compounds that: (a) can be used to treat disorders characterised
by aberrant EMI1 expression or activity, (b) bind to EMI1 protein or (c) inhibit interaction of
EMI1 with a target molecule.

ABEQ:
(11) processes for identifying compounds that: (a) can be used to treat disorders characterised
by aberrant EMI1 expression or activity, (b) bind to EMI1 protein or (c) inhibit interaction of
EMI1 with a target molecule.

29. Document ID: EP 889900 A1, WO 9825946 A1, AU 9854283 A

L7: Entry 29 of 44

File: DWPI

Jan 13, 1999

DERWENT-ACC-NO: 1998-348441
DERWENT-WEEK: 199907

TITLE: New isolated vascular endothelial cadherin-2 - used to develop products for modulating
angiogenesis, e.g. for treating tumours, glaucoma, psoriasis, inflammatory diseases or organ
transplantation

PRIORITY-DATA: 1996SE-0004731 (December 12, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 889900 A1				

January 13, 1999
E
000
C07H021/04
WO 9825946 A1
June 18, 1998
E
053
C07H021/04
AU 9854283 A
July 3, 1998
N/A
000
C07H021/04

APPLICATION-DATA:
PUB-NO
APPL-DATE
APPL-NO
DESCRIPTOR
EP 889900A1
November 5, 1997
1997EP-0948160
N/A
EP 889900A1
November 5, 1997
1997WO-US20006
N/A
EP 889900A1
WO 9825946
Based on
WO 9825946A1
November 5, 1997
1997WO-US20006
N/A
AU 9854283A
November 5, 1997
1998AU-0054283
N/A
AU 9854283A
WO 9825946
Based on

INT-CL (IPC): A01N 43/04; A61K 38/08; A61K 38/16; A61K 39/395; C07H 21/04; C07K 14/705; C07K 16/28; C12P 21/08

IN: DEJANA, E, TELO, P

AB: The following are claimed: (A) a glycosylated or unglycosylated protein comprises an amino acid sequence shown or a homologous sequence having at least 70% homology to this sequence; (B) a cDNA sequence coding for a protein as in (A); (C) a structural gene coding for a protein as in (A) or a peptide derived from the protein; (D) a recombinant protein or peptide expressed by a structural gene or a fragment of a gene as in (C); (E) an antibody binding specifically to a protein as in (A) or a part of the protein; (F) a modifier of the binding of a protein as in (A); (G) a diagnostic kit comprising as a diagnostic reagent an antibody as in (E) or a modifier as in (F); (H) a transgenic animal or cell overexpressing or lacking a protein as in (A); (I) an antisense oligonucleotide (ON) based on the cDNA sequence as in (B); (J) a monoclonal antibody (MAb) which specifically binds to a VE-cadherin and modifies angiogenesis; (K) a hybridoma cell line producing a MAb as in (J); (L) a polypeptide which comprises an amino acid sequence which is the same as the amino acid sequence of the variable region of a MAb as in (J); (M) a nucleic acid that encodes a polypeptide as in (L); (N) a polypeptide which comprises an amino acid sequence which is the same as the amino acid sequence of the hypervariable region of a MAb as in (J); (O) a nucleic acid that encodes a polypeptide as in (N); (P) a humanised antibody or a fragment comprising a polypeptide as in (N); (Q) modifiers that specifically bind to an amino acid sequence TIDLRYMSP, and (R) a synthetic peptide comprising an amino acid sequence TIDLRYMSP and is capable of affecting angiogenesis., The products can be used with a chemotherapeutic agent, e.g. doxorubicin, cisplatin and taxol., USE - The novel polypeptides are vascular endothelial cadherins (designated VE-cadherin-2) which promote cell-to-cell homotypic adhesion and their expression is upregulated in proliferating endothelial cells in comparison to resting cells. The products can be used for inhibiting angiogenesis and inhibiting pathological conditions such as tumours, neovascular glaucoma, proliferative retinopathy including proliferative diabetic retinopathy, macular degeneration, hemangiomas, angiofibromas, and psoriasis. They can also be used for the prevention or inhibition of leukocyte infiltration, tumour cell metastasis, or endothelial permeability, as vaccines and for making endothelial junctions more permeable to antigens, thus indicating use of the modifiers for treatment or prevention of acute and chronic inflammatory diseases, organ transplantation, myocardial ischaemia, atherosclerosis, rheumatoid arthritis and intestinal infection. The products can also be used for detection, diagnosis and drug screening.

L7: Entry 29 of 44
File: DWPI
Jan 13, 1999

DERWENT-ACC-NO: 1998-348441
DERWENT-WEEK: 199907

TITLE: New isolated vascular endothelial cadherin-2 - used to develop products for modulating angiogenesis, e.g. for treating tumours, glaucoma, psoriasis, inflammatory diseases or organ transplantation

ABTX:
The following are claimed: (A) a glycosylated or unglycosylated protein comprises an amino acid sequence shown or a homologous sequence having at least 70% homology to this sequence; (B) a cDNA sequence coding for a protein as in (A); (C) a structural gene coding for a protein as in (A) or a peptide derived from the protein; (D) a recombinant protein or peptide expressed by a structural gene or a fragment of a gene as in (C); (E) an antibody binding specifically to a protein as in (A) or a part of the protein; (F) a modifier of the binding of a protein as in (A); (G) a diagnostic kit comprising as a diagnostic reagent an antibody as in (E) or a modifier as in (F); (H) a transgenic animal or cell overexpressing or lacking a protein as in (A); (I) an antisense oligonucleotide (ON) based on the cDNA sequence as in (B); (J) a monoclonal antibody (MAb) which specifically binds to a VE-cadherin and modifies angiogenesis; (K) a hybridoma cell line producing a MAb as in (J); (L) a polypeptide which comprises an amino acid sequence which is the same as the amino acid sequence of the variable region of a MAb as in (J); (M) a nucleic acid that encodes a polypeptide as in (L); (N) a polypeptide which comprises an

amino acid sequence
which is the same as the amino acid sequence of the hypervariable region of a MAb as in (J); (O)
a nucleic acid that encodes a polypeptide as in (N); (P) a humanised antibody or a fragment
comprising a polypeptide as in (N); (Q) modifiers that specifically bind to an amino acid
sequence TIDLRYMSP, and (R) a synthetic peptide comprising an amino acid sequence TIDLRYMSP and
is capable of affecting angiogenesis.

30. Document ID: JP 2000511411 W, WO 9741151 A2, AU 9728182 A, EP 912608 A2
L7: Entry 30 of 44
File: DWPI
Sep 5, 2000

DERWENT-ACC-NO: 1997-549682
DERWENT-WEEK: 200047

TITLE: New isolated streptococcal choline binding proteins - used to develop products for
treating or preventing bacterial infection and for detection, diagnosis and screening

PRIORITY-DATA: 1996US-0642250 (May 1, 1996), 1996US-0016632 (May 1, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
JP 2000511411 W	September 5, 2000	N/A	132	C12N015/09
WO 9741151 A2	November 6, 1997	E	142	C07K014/315
AU 9728182 A	November 19, 1997	N/A	000	C07K014/315
EP 912608 A2	May 6, 1999	E	000	C07K014/315

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
JP2000511411W	May 1, 1997	1997JP-0539170	N/A
JP2000511411W	May 1, 1997	1997WO-US07198	N/A
JP2000511411W		WO 9741151	Based on
WO 9741151A2	May 1, 1997	1997WO-US07198	N/A
AU 9728182A	May 1, 1997	1997AU-0028182	N/A
AU 9728182A		WO 9741151	Based on
EP 912608A2	May 1, 1997	1997EP-0922539	N/A
EP 912608A2	May 1, 1997	1997WO-US07198	N/A
EP 912608A2		WO 9741151	Based on

INT-CL (IPC): A61K 31/14; A61K 31/197; A61K 38/00; A61K 38/43; A61K 39/09; A61K 39/395; A61K 45/00; A61K
48/00; A61P 11/00; A61P 31/04; C07K 14/315; C07K 16/12; C12N 1/21; C12N 5/10; C12N 15/02; C12N 15/09; C12P
21/08 ; C12Q 1/68; G01N 33/53; G01N 33/569; G01N 33/577

IN: MASURE, H R, ROSENOW, C I, TUOMANEN, E, WIZEMAN, T M

AB: A new streptococcal choline binding protein (SCBP) has the following
characteristics:(a) choline-binding activity; and (b) elution from a chromatographic column
in the presence of at least about 10% choline; with the proviso that the SCBP is not PspA or
autolysin (LytA)., Also claimed are: (1) a SCBP having either a 420 or 631 amino acid (aa)
sequence given in the specification; (2) a purified (monoclonal) antibody to SCBP; (3) an
immortal cell line that produces a monoclonal antibody (MAb) as in (2); (4) a purified
(recombinant) nucleic acid (I) which encodes an SCBP as described above (sequences given in
the specification), or a fragment of at least 15 nucleotides; (5) (I) operatively linked to
an expression control sequence; (6) an oligonucleotide prepared from (I) that is capable of
screening for nucleic acid encoding SCBP in alternate species; (7) a unicellular host
transformed with a recombinant DNA molecule as in (5); (8) a pharmaceutical composition
comprising an inhibitor of streptococcal adhesion to fibronectin selected from a peptide of
not more than 15 amino acid residues containing the aa sequence WQPPRARI, an enolase, and an
antibody specific for the aa sequence WQPPRARI; (9) a method for treating infection with a
bacterium that expressed a SCBP comprising administering a hindered cationic small molecule
that inhibits streptococcal adhesion to fibronectin; (10) a method for treating infection
with a bacterium that expresses an SCBP comprising administering pulmonarily an adhesion
inhibitory agent selected from: (a) an SCBP with the proviso that the SCBP is not PspA or
autolysin (LytA); (b) an antibody to a choline binding protein; (c) an enolase; (d) a
hindered cationic small molecule; (e) the peptide WQPPRARI; and (f) an antibody specific for
an epitope having the aa sequence WQPPRARI., USE - The SCBPs can be used in vaccines. They
can be used for treating or preventing bacterial infection. They can also

be used for
screening, detection and diagnosis. The antibodies can be used for passive immunisation,
diagnostics, or screening.

L7: Entry 30 of 44
File: DWPI
Sep 5, 2000

DERWENT-ACC-NO: 1997-549682
DERWENT-WEEK: 200047

TITLE: New isolated streptococcal choline binding proteins - used to develop products for
treating or preventing bacterial infection and for detection, diagnosis and screening

ABTX:
Also claimed are: (1) a SCBP having either a 420 or 631 amino acid (aa) sequence given in the
specification; (2) a purified (monoclonal) antibody to SCBP; (3) an immortal cell line that
produces a monoclonal antibody (MAb) as in (2); (4) a purified (recombinant) nucleic acid (I)
which encodes an SCBP as described above (sequences given in the specification), or a fragment of
at least 15 nucleotides; (5) (I) operatively linked to an expression control sequence; (6) an
oligonucleotide prepared from (I) that is capable of screening for nucleic acid encoding SCBP in
alternate species; (7) a unicellular host transformed with a recombinant DNA molecule as in (5);
(8) a pharmaceutical composition comprising an inhibitor of streptococcal adhesion to fibronectin
selected from a peptide of not more than 15 amino acid residues containing the aa sequence
WQPPRARI, an enolase, and an antibody specific for the aa sequence WQPPRARI; (9) a method for
treating infection with a bacterium that expressed a SCBP comprising administering a hindered
cationic small molecule that inhibits streptococcal adhesion to fibronectin; (10) a method for
treating infection with a bacterium that expresses an SCBP comprising administering pulmonarily
an adhesion inhibitory agent selected from: (a) an SCBP with the proviso that the SCBP is not
PspA or autolysin (LytA); (b) an antibody to a choline binding protein; (c) an enolase; (d) a
hindered cationic small molecule; (e) the peptide WQPPRARI; and (f) an antibody specific for an
epitope having the aa sequence WQPPRARI.

31. Document ID: WO 9736614 A1, AU 9724293 A
L7: Entry 31 of 44
File: DWPI
Oct 9, 1997

DERWENT-ACC-NO: 1997-549326
DERWENT-WEEK: 199750

TITLE: Use of crosslinked Staphylococcal protein A - for treating auto-immune diseases,
transplant rejection neoplastic diseases or infectious disease such as HIV infection

PRIORITY-DATA: 1996US-0024802 (March 29, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9736614 A1	October 9, 1997	E	100	A61K039/09
AU 9724293 A	October 22, 1997	N/A	000	A61K039/09

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
WO 9736614A1	March 28, 1997	1997WO-US05277	N/A
AU 9724293A	March 28, 1997	1997AU-0024293	N/A
AU 9724293A		WO 9736614	Based on

INT-CL (IPC): A61K 39/02; A61K 39/04; A61K 39/09; A61K 45/00; A61K 47/04; C07K 14/24; C07K 14/315; C07K 14/35; C07K 17/02; C07K 17/06; C07K 17/14

IN: REISER, R F, TERMAN, D S

AB: The following are claimed: (A) a composition useful for treating an autoimmune or
neoplastic disease and comprising a mixture of monomeric and crosslinked polymeric protein A
molecules or a functional derivative of a protein A molecule, where: (a) the cross-linked
polymer molecule comprises at least 2 monomeric units of protein A or of the functional
derivative, and (b) at least 10% of the total protein A or functional derivative in the form
of polymers; (B) a composition useful for treating an autoimmune or neoplastic disease
comprising a chemically crosslinked polymer of protein A, or of a functional derivative of
protein A, and having the following characteris tics: (a) immunoglobulin Fc binding activity
is less than half that of native protein A, and (b) immunoglobulin V(H)3 region binding is
more than twice that of native protein A; (C) a method of extracorporea l treatment of a
subject having an autoimmune or neoplastic disease, where, over a course of one or more
treatments, plasma of the subject is perfused through a protein A-silica immunoadsorbent
column to produce a perfusate, and the perfusate is reinfused to the subject; the
improvement comprising: (a) over the course of one or more treatments, perfusing plasma of
the subject through the column; (b) at each treatment, measuring the amount of protein A in
the perfusate prior to the reinfusing; (c) when the amount of total protein A in the
perfusate is < 2 mu g, increasing the volume of the perfusate or increasing the number of
doses of the perfusate such that the subject receives 2-200 mu g per treatment; (d) when the

amount of total protein A in the perfusate is > 200 mu g, decreasing the volume of the
perfusate such that the subject receives 2-200 mu g per treatment; (D) a method of
extracorporeal treatment of a subject having an autoimmune or neoplastic disease where, over
a course of one or more treatments, plasma of the subject is perfused through a protein
A-silica immunoadsorbent column to produce a perfusate, and the perfusate is reinfused to
the subject, the improvement comprising: (a) over the course of one or more treatments,
perfusing plasma of the subject through the column; (b) at each treatment, measuring the
amount of bacterial enterotoxins in the perfusate prior to the reinfusing; (c) when the
amount of total bacterial enterotoxins in the perfusate is < 1 ng, increasing the volume of
the perfusate or increasing the number of doses of the perfusate such that the subject
receives 1-200 ng per treatment; (d) when the amount of total bacterial enterotoxins in the
perfusate is > 200 ng, decreasing the volume of the perfusate such that the subject receives
1-200 ng per treatment;, and (E) a method for reducing toxicity of monomeric enterotoxin
molecules by mixing the enterotoxin molecules with protein A, adding a crosslinking agent
capable of crosslinking the enterotoxin molecules and protein A and allowing any enterotoxin
to be chemically crosslinked with the protein A, thereby reducing the toxicity., In (A), the
polymers have a range of molecular masses 12-10 000 (preferably 64-1000) kDa and at least 50
% of the total protein A or functional derivative is in the form of polymers. The protein A
is complexed with IgG and complement components to form protein A-immunoglobulin-complement
complexes. The IgG is a monoclonal antibody. The protein A is further crosslinked with
molecules of a bacterial superantigen or its functional derivative to form a mixture of: (i)
protein A-superantigen; (ii) protein A functional derivative-superanti gen; (iii) protein
A-superantigen functional derivative, or (iv) protein A functional derivative-superantigen
functional derivative, and (c) polymeric crosslinked superantigen or superantigen functional
derivative. The bacterial superantigen is selected from: enterotoxin of Staphylococcus
aureus, toxic shock syndrome toxin, a Streptococcus pyrogenic exotoxin, etc. The
crosslinking is with e.g. 1-cyclohexyl-3-(2-m orpholinyl-(4-ethyl)carbodiimide., USE - The
crosslinked Staphylococcal protein A (SpA) readily combines with IgG in host plasma to form
complexes which bind to and block the FcR on macrophages, lymphocytes and platelets. The
compositions can be used for treating autoimmune diseases such as idiopathic
thrombocytopenic purpura, rheumatoid arthritis, systemic lupus erythematos us, myasthenia
gravis, multiple sclerosis, Alzheimer's disease, Type I diabetes mellitus, sarcoidosis,
vernal conjunctivitis, glomerulonep hritis, pemphigus vulgaris, chronic active hepatitis,
primary biliary cirrhosis, dermatitis, asthma, transplant rejection, paraneoplastic syndrome
or haemolytic anaemia, neoplastic diseases such as carcinomas of the breast, lung, colon or
kidney, melanomas, lymphomas or leukaemias and infectious diseases. The compositions can
also be used in HIV disorders to prevent gp 120 induced programming of B and T cells for
apoptosis. The compositions can laso be used in vitro to test products, monitor therapy, and
diagnose diseases associated with abnormal function of Fc receptors or abnormal processing
of immune complexes or FcR-binding structures., ADVANTAGE - The complexes are extremely
efficient in FcR blocking and can achieve pharmacologic effects at relatively low doses. In
the extracorporeal methods, by prescribing the amount of SpA infused, the method avoids
toxicity and improves the therapeutic index.

L7: Entry 31 of 44

File: DWPI

Oct 9, 1997

DERWENT-ACC-NO: 1997-549326
DERWENT-WEEK: 199750

TITLE: Use of crosslinked Staphylococcal protein A - for treating auto-immune diseases,
transplant rejection neoplastic diseases or infectious disease such as HIV infection

ABTX:
The following are claimed: (A) a composition useful for treating an autoimmune or neoplastic
disease and comprising a mixture of monomeric and crosslinked polymeric protein A molecules or a
functional derivative of a protein A molecule, where: (a) the cross-linked polymer molecule
comprises at least 2 monomeric units of protein A or of the functional derivative, and (b) at
least 10% of the total protein A or functional derivative in the form of polymers; (B) a
composition useful for treating an autoimmune or neoplastic disease comprising a chemically
crosslinked polymer of protein A, or of a functional derivative of protein A, and having the
following characteris tics: (a) immunoglobulin Fc binding activity is less than half that of
native protein A, and (b) immunoglobulin V(H)3 region binding is more than twice that of native
protein A; (C) a method of extracorporea l treatment of a subject having an autoimmune or
neoplastic disease, where, over a course of one or more treatments, plasma of the subject is
perfused through a protein A-silica immunoadsorbent column to produce a perfusate, and the
perfusate is reinfused to the subject; the improvement comprising: (a) over the course of one or
more treatments, perfusing plasma of the subject through the column; (b) at each treatment,
measuring the amount of protein A in the perfusate prior to the reinfusing; (c) when the amount
of total protein A in the perfusate is < 2 mu g, increasing the volume of the perfusate or
increasing the number of doses of the perfusate such that the subject receives 2-200 mu g per
treatment; (d) when the amount of total protein A in the perfusate is > 200 mu g, decreasing the
volume of the perfusate such that the subject receives 2-200 mu g per treatment; (D) a method of
extracorporeal treatment of a subject having an autoimmune or neoplastic disease where, over a
course of one or more treatments, plasma of the subject is perfused through a protein A-silica
immunoadsorbent column to produce a perfusate, and the perfusate is reinfused to the subject, the
improvement comprising: (a) over the course of one or more treatments, perfusing plasma of the
subject through the column; (b) at each treatment, measuring the amount of bacterial enterotoxins
in the perfusate prior to the reinfusing; (c) when the amount of total bacterial enterotoxins in
the perfusate is < 1 ng, increasing the volume of the perfusate or increasing the number of doses
of the perfusate such that the subject receives 1-200 ng per treatment; (d) when the amount of

total bacterial enterotoxins in the perfusate is > 200 ng, decreasing the volume of the perfusate
such that the subject receives 1-200 ng per treatment;, and (E) a method for reducing toxicity of
monomeric enterotoxin molecules by mixing the enterotoxin molecules with protein A, adding a
crosslinking agent capable of crosslinking the enterotoxin molecules and protein A and allowing
any enterotoxin to be chemically crosslinked with the protein A, thereby reducing the toxicity.

32. Document ID: KR 99082173 A, WO 9728446 A1, AU 9722422 A, EP 922222 A1, JP 2000504114 W
L7: Entry 32 of 44
File: DWPI
Nov 25, 1999

DERWENT-ACC-NO: 1997-402745
DERWENT-WEEK: 200055

TITLE: Detection and evaluation of bladder cancer - by quantitation of amounts of hyaluronic acid
or hyaluronidase in samples such as blood, tissue extract or urine

PRIORITY-DATA: 1996US-0010976 (February 1, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
KR 99082173 A	November 25, 1999	N/A	000	G01N033/53
WO 9728446 A1	August 7, 1997	E	126	G01N033/53
AU 9722422 A	August 22, 1997	N/A	000	G01N033/53
EP 922222 A1	June 16, 1999	E	000	G01N033/53
JP 2000504114 W	April 4, 2000	N/A	089	G01N033/574

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
KR 99082173A	January 31, 1997	1997WO-US00546	N/A
KR 99082173A	July 31, 1998	1998KR-0705898	N/A
KR 99082173A		WO 9728446	Based on
WO 9728446A1	January 31, 1997	1997WO-US00546	N/A
AU 9722422A	January 31, 1997	1997AU-0022422	N/A
AU 9722422A	January 31, 1997	1997WO-US00546	N/A
AU 9722422A		WO 9728446	Based on
EP 922222A1	January 31, 1997	1997EP-0905574	N/A
EP 922222A1	January 31, 1997	1997WO-US00546	N/A
EP 922222A1		WO 9728446	Based on
JP2000504114W	January 31, 1997	1997JP-0527660	N/A
JP2000504114W	January 31, 1997	1997WO-US00546	N/A
JP2000504114W		WO 9728446	Based on

INT-CL (IPC): A01N 47/40; A01N 47/46; A01N 47/48; A61K 31/21; A61K 31/26; C12Q 1/34; G01N 33/15; G01N 33/53; G01N 33/537 ; G01N 33/573; G01N 33/574

IN: BLOCK, N L, LOKESHWAR, V B, PHAM, H T

AB: The following are claimed: (A) screening for bladder cancer (BC), comprising: (a)
obtaining a sample from a person suspected of having BC; (b) quantitating an normalising the
amount of hyaluronic acid (HA) in the sample; and (c) comparing the normalised amount of HA
to a cut-off limit of HA for having BC, thus identifying the person as having increased risk
of BC when the normalised amount of HA is greater than the cut-off limit of HA; (B)
screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC;
(b) quantitating an normalising the amount of hyaluronidase (HE) in the sample; and (c)
comparing the normalised amount of HE to a cut-off limit of HE for having BC, thus
identifying the person as having increased risk of BC when the normalised amount of HE is
greater than the cut-off limit of HE; (C) differentiating BC by grade, comprising: (a)
obtaining a sample from a person suspected of having BC; (b) quantitating and normalising
the amount of HA in the sample; (c) quantitating and normalising the amount of HE in the
sample; (d) comparing the normalised amount of HA to a cut-off limit of HA for having BC;
(e) comparing the normalised amount of HE to a cut-off limit of HE for having BC; and (f)

identifying the person as having low-grade BC when the normalised amount of HA is greater than the cut-off limit of HA and the normalised amount of HE is less than the cut-off limit of HE, or identifying the person as having intermediate-grade or high grade BC when the normalised amount of HE is greater than the cut off limit of HE; (D) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) separating HA and/or HE in the sample to obtain a size profile; and (c) identifying the person as having increased risk for BC based on the size profile; (E) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) adding the sample to a cell culture; and (c) identifying the person as having increased risk of BC by proliferation of the cell culture; (F) diagnostic kit for detection of BC, comprising: (a) HA; (b) HA binding protein; and (c) ancillary reagents suitable for quantitating HA and/or HE in a sample of biological fluid. Components (a), (b) and (c) are in separate containers; (G) composition comprising an enriched fraction of HE p65 or p55; (H) composition comprising a HA fragment generated by the HE described in (E); (I) composition comprising an antibody to the HE of (E) above; and (J) composition comprising an enriched fraction of HA derived from the urine of a person with BC., USE - The processes utilise the new discovery that HA and HE are diagnostic markers for the detection of bladder cancer (e.g. transitional cell carcinoma, squamous carcinoma and adenocarcinoma), evaluation of its grade, and monitoring the efficacy of its treatment., ADVANTAGE - Measurements of HA and HE levels are simple and are non-invasive, and typically require only a HA-binding protein which can be purified in large quantities.

L7: Entry 32 of 44

File: DWPI

Nov 25, 1999

DERWENT-ACC-NO: 1997-402745
DERWENT-WEEK: 200055

TITLE: Detection and evaluation of bladder cancer - by quantitation of amounts of hyaluronic acid or hyaluronidase in samples such as blood, tissue extract or urine

ABTX:
The following are claimed: (A) screening for bladder cancer (BC), comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating an normalising the amount of hyaluronic acid (HA) in the sample; and (c) comparing the normalised amount of HA to a cut-off limit of HA for having BC, thus identifying the person as having increased risk of BC when the normalised amount of HA is greater than the cut-off limit of HA; (B) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating an normalising the amount of hyaluronidase (HE) in the sample; and (c) comparing the normalised amount of HE to a cut-off limit of HE for having BC, thus identifying the person as having increased risk of BC when the normalised amount of HE is greater than the cut-off limit of HE; (C) differentiating BC by grade, comprising: (a) obtaining a sample from a person suspected of having BC; (b) quantitating and normalising the amount of HA in the sample; (c) quantitating and normalising the amount of HE in the sample; (d) comparing the normalised amount of HA to a cut-off limit of HA for having BC; (e) comparing the normalised amount of HE to a cut-off limit of HE for having BC; and (f) identifying the person as having low-grade BC when the normalised amount of HA is greater than the cut-off limit of HA and the normalised amount of HE is less than the cut-off limit of HE, or identifying the person as having intermediate-grade or high grade BC when the normalised amount of HE is greater than the cut off limit of HE; (D) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) separating HA and/or HE in the sample to obtain a size profile; and (c) identifying the person as having increased risk for BC based on the size profile; (E) screening for BC, comprising: (a) obtaining a sample from a person suspected of having BC; (b) adding the sample to a cell culture; and (c) identifying the person as having increased risk of BC by proliferation of the cell culture; (F) diagnostic kit for detection of BC, comprising: (a) HA; (b) HA binding protein; and (c) ancillary reagents suitable for quantitating HA and/or HE in a sample of biological fluid. Components (a), (b) and (c) are in separate containers; (G) composition comprising an enriched fraction of HE p65 or p55; (H) composition comprising a HA fragment generated by the HE described in (E); (I) composition comprising an antibody to the HE of (E) above; and (J) composition comprising an enriched fraction of HA derived from the urine of a person with BC.

33. Document ID: AU 707349 B, WO 9605303 A1, AU 9532723 A, EP 777731 A1, US 5695993 A, US 5852171 A

L7: Entry 33 of 44

File: DWPI

Jul 8, 1999

DERWENT-ACC-NO: 1996-139699
DERWENT-WEEK: 199938

TITLE: Isolated endothelial cell protein C/activated protein C receptor - used to inhibit inflammatory responses, screen for cpds. which alter receptor binding and, by blocking receptor binding, enhance inflammatory response

PRIORITY-DATA: 1994US-0289699 (August 12, 1994), 1997US-0878283 (June 18, 1997)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 707349 B	July 8, 1999	N/A	000	C12N015/12
WO 9605303 A1	February 22, 1996	E	058	C12N015/12
AU 9532723 A				

March 7, 1996
N/A
000
C12N015/12
EP 777731 A1
June 11, 1997
E
000
C12N015/12
US 5695993 A
December 9, 1997
N/A
028
C12N005/16
US 5852171 A
December 22, 1998
N/A
000
C07K014/705

APPLICATION-DATA:
PUB-NO
APPL-DATE
APPL-NO
DESCRIPTOR
AU 707349B
August 9, 1995
1995AU-0032723
N/A
AU 707349B
AU 9532723
Previous Publ.
AU 707349B
WO 9605303
Based on
WO 9605303A1
August 9, 1995
1995WO-US09636
N/A
AU 9532723A
August 9, 1995
1995AU-0032723
N/A
AU 9532723A
WO 9605303
Based on
EP 777731A1
August 9, 1995
1995EP-0929335
N/A
EP 777731A1
August 9, 1995
1995WO-US09636
N/A
EP 777731A1
WO 9605303
Based on
US 5695993A
August 12, 1994
1994US-0289699
N/A
US 5852171A
August 12, 1994
1994US-0289699
Div ex
US 5852171A
June 18, 1997
1997US-0878283
N/A
US 5852171A
US 5695993
Div ex

INT-CL (IPC): A61K 38/17; A61K 39/395; C07H 21/04; C07K 14/705; C07K 16/28; C12N 5/16; C12N 15/11; C12N 15/12; G01N 33/68

IN: ESMON, C T; FUKUDOME, K

AB: Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new.

Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours., Isolated endothelial cell protein C/activated protein C receptor (EPCR) is new. Also claimed are: (1) a nucleotide sequence encoding EPCR; and (2) an antibody or fragment specifically immunoreactive with a unique epitope of EPCR., USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours.

L7: Entry 33 of 44

File: DWPI

Jul 8, 1999

DERWENT-ACC-NO: 1996-139699
DERWENT-WEEK: 199938
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TITLE: Isolated endothelial cell protein C/activated protein C receptor - used to inhibit inflammatory responses, screen for cpds. which alter receptor binding and, by blocking receptor binding, enhance inflammatory response

ABTX:
USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours.

ABEQ:
USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours.

ABEQ:
USE - EPCR and substances which up-regulate its expression are useful to inhibit inflammatory responses (claimed). This inhibition is useful in the treatment of, e.g. Gram-negative sepsis, stroke, thrombosis, septic shock, ARDS and pulmonary emboli. EPCR is also useful to screen for cpds. which alter its binding to (activated) protein C (claimed). Localising EPCR to surfaces in contact with blood will render the surfaces anticoagulant as EPCR binds and concentrates the anticoagulant activated protein C at the surface. Its function can also be enhanced by overexpressing EPCR in endothelium that could be used to coat vascular grafts in patients with vascular disease, or in stents in cardiac patients. Using blocking cpds. to prevent (activated) protein C binding to EPCR it is possible to enhance an inflammatory response and so treat solid tumours.

34. Document ID: AU 710106 B, WO 9534652 A1, AU 9528229 A, EP 804580 A1, JP 10504186 W

L7: Entry 34 of 44

File: DWPI

Sep 16, 1999

DERWENT-ACC-NO: 1996-049681
DERWENT-WEEK: 199950
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TITLE: Calcium-binding monoclonal antibody immunoreactive with Protein C - inhibits Protein C anticoagulant activation by thrombin-thrombomodulin, e.g. for treating tumours

PRIORITY-DATA: 1994US-0259321 (June 10, 1994)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 710106 B	September 16, 1999	N/A	000	C12N015/13
WO 9534652 A1	December 21, 1995	E	041	C12N015/13
AU 9528229 A	January 5, 1996	N/A	000	C12N015/13
EP 804580 A1	November 5, 1997	E	000	C12N015/13
JP 10504186 W	April 28, 1998	N/A	038	C12N015/09

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 710106B	June 9, 1995	1995AU-0028229	N/A
AU 710106B		AU 9528229	Previous Publ.
AU 710106B		WO 9534652	Based on
WO 9534652A1	June 9, 1995	1995WO-US07372	N/A
AU 9528229A	June 9, 1995	1995AU-0028229	

N/A
AU 9528229A
WO 9534652
Based on
EP 804580A1
June 9, 1995
1995EP-0923791
N/A
EP 804580A1
June 9, 1995
1995WO-US07372
N/A
EP 804580A1
WO 9534652
Based on
JP 10504186W
June 9, 1995
1995WO-US07372
N/A
JP 10504186W
June 9, 1995
1996JP-0502358
N/A
JP 10504186W
WO 9534652
Based on

INT-CL (IPC): A61K 33/06; A61K 38/00; A61K 38/19; A61K 39/395; A61K 39/395; C07K 16/40; C07K 16/46; C07K 17/00; C12N 15/09; C12N 15/13; C12P 21/08; A61K 33/06; A61K 39/395; C12P 21/08; C12R 1/91; A61K 33/06; A61K 39/395; A61K 38/19; A61K 39/395

IN: ESMON, C T, REZAIE, A

AB: A recombinant Ca2+ dependent monoclonal antibody (mAb) immunoreactive with an epitope in the activation peptide region of the heavy chain of Protein C defined by (I), EDQVDPRLIDKG (1) in combination with calcium, which inhibits protein C activation by thrombin-thrombomodulin, is claimed., USE - The mAb (opt. with a cytokine, or a cytokine expression inhibitor to coagulate microvasculature in tumours, but not in the absence of the mAb) can be used to inhibit Protein C anticoagulant activation by thrombin-thrombomodulin (claimed), useful in the treatment of tumour patients. The mAb can be also be used in diagnostic assays (opt. bound to a detectable label), for mimicking HPC-4 Protein C binding and when immobilised on a substrate to purify Protein C from a biological fluid (claimed).

L7: Entry 34 of 44
File: DWPI
Sep 16, 1999

DERWENT-ACC-NO: 1996-049681
DERWENT-WEEK: 199950

TITLE: Calcium-binding monoclonal antibody immunoreactive with Protein C - inhibits Protein C anticoagulant activation by thrombin-thrombomodulin, e.g. for treating tumours

ABTX:
USE - The mAb (opt. with a cytokine, or a cytokine expression inhibitor to coagulate microvasculature in tumours, but not in the absence of the mAb) can be used to inhibit Protein C anticoagulant activation by thrombin-thrombomodulin (claimed), useful in the treatment of tumour patients. The mAb can be also be used in diagnostic assays (opt. bound to a detectable label), for mimicking HPC-4 Protein C binding and when immobilised on a substrate to purify Protein C from a biological fluid (claimed).

35. Document ID: US 5446132 A
L7: Entry 35 of 44
File: DWPI
Aug 29, 1995

DERWENT-ACC-NO: 1995-310936
DERWENT-WEEK: 199851

TITLE: New thrombin activated platelet protein-2 - and specific antibodies for e.g. detecting activated platelets or thromboses and targetting therapeutic agents for treating thrombosis

PRIORITY-DATA: 1991US-0086472 (October 1, 1991), 1991US-0768043 (January 10, 1991)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5446132 A	August 29, 1995	N/A	017	C07K014/435

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 5446132A	January 10, 1991	1991US-0768043	CIP of
US 5446132A	October 1, 1991	1991US-0086472	N/A

INT-CL (IPC): C07K 14/435; C07K 14/46; C07K 14/47; C07K 14/52

IN: MATSUEDA, G R, REED, G L

AB: Pure protein, designated thrombin-activated platelet protein-2 (TAPP-2), that is selectively expressed on the surface of thrombin-activated platelets is new. It has mol.wt. 120 kDa and is recognised by an antibody with the binding specificity of 12A7., USE - TAPP-2 and the unclaimed protein TAPP-1 are indicators of platelet activation, so that their presence is indicative of a blood clot. Antibodies (Abs) and their fragments are useful in immunoassays, for in vivo imaging of thromboses or to target immuno-diagnostic or immuno-therapeutic agents to thromboses (e.g. using a chimaera comprising an antigen-binding fragment plus a thrombolytic agent, thrombin inhibitor, activated protein C etc.). Typical applications are the treatment of e.g. pulmonary thromboembolism, deep

venous thrombosis and
renal vein or peripheral arterial thrombosis. Abs are administered at 0.001-50 (esp. 1-10)
picomole/ml, e.g. given orally, intranasally or by injection.

L7: Entry 35 of 44
File: DWPI
Aug 29, 1995

DERWENT-ACC-NO: 1995-310936
DERWENT-WEEK: 199851

TITLE: New thrombin activated platelet protein-2 - and specific antibodies for e.g. detecting
activated platelets or thromboses and targetting therapeutic agents for treating thrombosis

ABTX:
USE - TAPP-2 and the unclaimed protein TAPP-1 are indicators of platelet activation, so that
their presence is indicative of a blood clot. Antibodies (Abs) and their fragments are useful in
immunoassays, for in vivo imaging of thromboses or to target immuno-diagnostic or
immuno-therapeutic agents to thromboses (e.g. using a chimaera comprising an antigen-binding
fragment plus a thrombolytic agent, thrombin inhibitor, activated protein C etc.). Typical
applications are the treatment of e.g. pulmonary thromboembolism, deep venous thrombosis and
renal vein or peripheral arterial thrombosis. Abs are administered at 0.001-50 (esp. 1-10)
picomole/ml, e.g. given orally, intranasally or by injection.

36. Document ID: AU 687116 B, WO 9511314 A1, AU 9480989 A, US 5445937 A, EP 728216 A1, JP 09504611 W
L7: Entry 36 of 44
File: DWPI
Feb 19, 1998

DERWENT-ACC-NO: 1995-170233
DERWENT-WEEK: 199824

TITLE: Aiding the diagnosis of Alzheimer's disease - comprises detecting a disease-specific
biochemical marker macromolecule within a cerebro-spina l fluid or serum sample

PRIORITY-DATA: 1993US-0138109 (October 20, 1993), 1991US-0812826 (December 24, 1991)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
AU 687116 B	February 19, 1998	N/A	000	C12Q001/68
WO 9511314 A1	April 27, 1995	E	067	C12Q001/68
AU 9480989 A	May 8, 1995	N/A	000	C12Q001/68
US 5445937 A	August 29, 1995	N/A	026	C12Q001/68
EP 728216 A1	August 28, 1996	E	000	C12Q001/68
JP 09504611 W	May 6, 1997	N/A	055	G01N033/68

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
AU 687116B	October 19, 1994	1994AU-0080989	N/A
AU 687116B		AU 9480989	Previous Publ.
AU 687116B		WO 9511314	Based on
WO 9511314A1	October 19, 1994	1994WO-US11929	N/A
AU 9480989A	October 19, 1994	1994AU-0080989	N/A
AU 9480989A		WO 9511314	Based on
US 5445937A	December 24, 1991	1991US-0812826	CIP of
US 5445937A	October 20, 1993	1993US-0138109	N/A
US 5445937A		US 5272055	CIP of
EP 728216A1	October 19, 1994	1994EP-0931414	N/A
EP 728216A1	October 19, 1994	1994WO-US11929	N/A
EP 728216A1		WO 9511314	Based on
JP09504611W	October 19, 1994	1994WO-US11929	N/A
JP09504611W	October 19, 1994	1995JP-0512188	N/A

JP09504611W

WO 9511314

Based on

INT-CL (IPC): C12Q 1/68; G01N 33/573; G01N 33/574; G01N 33/68

IN: HALEY, B E

AB: The following are claimed: (1) a method for aiding in the diagnosis of
Alzheimer's disease (AD) in a mammal comprising: (a) contacting in the presence of Mn2+ ion
a cerebrospinal fluid (CSF) sample which contains a nucleotide binding protein having an
apparent mol. wt. of approx. 42000 daltons, where the protein is glutamine synthetase, with
an effective amt. of a labelled ATP- or GTP-analogue photoaffinity-la belling reagent which
specifically binds the nucleotide binding protein at the nucleotide binding site to
photoaffinity label the nucleotide protein; (b) detecting the presence of glutamine
synthetase-Ab complexes; and (c) correlating the presence of such complexes with the
presence of AD; and (2) methods for aiding in the diagnosis of cancer in a mammal,
comprising: (a) contacting a fluid which contains nucleotide binding proteins having
apparent mol. wts. of approx. 14 000-15 000, 16 000, 24 000 and 120 000 daltons, with an
effective amt. of a labelled ATP- or GTP-analogue photoaffinity-labelli ng reagent which
specifically binds the nucleotide binding protein at the nucleotide binding site to
photoaffinity label the nucleotide protein; (b) fractionating the fluid sample to separate
the photoaffinity- labelled nucleotide binding protein; (c) detecting the presence of the
separated photoaffinity-labelled nucleotide binding protein in normal patients and the
absence of the photoaffinity-labelled nucleotide protein in other patients; and (d)
correlating the absence of the photo-affinity labelled nucleotide protein to the presence of
the relevant disease in the other patients., USE - The methods provide a means of accurately
diagnosing AD and cancer esp. leukaemia. The methods may also be used to detect epilepsy,
scrapies-type disorders, amytrophic lateral sclerosis, Down's syndrome, Behcet disease,
encephalitis, Huntingdon's disease, Creutzfeldt-Jakob disease, Parkinson's disease, AIDS
dementia, multi-infarct dementia, dystonia, ataxia, schizophrenia, neurosyphilis, cerebral
toxoplasmosis, brain irradiation, brain tumour, Guillain-Barre syndrome, tremor, multiple
sclerosis, head trauma, acute and chronic encephalitic, vascular disease and eating
disorders such as anorexia., ADVANTAGE - The methods incorporate a dual system of comparison
in order to diagnose the disease state. Diagnosis is based on both the presence of a unique
disease-specific binding protein or biochemical marker in a sample of body fluid from a
diseased patient, and the absence of a "normal" binding protein or biochemical marker
characterist ically found in samples from normal subjects. The method provides a reliable,
accurate, safe and effective method to detect disease-specific biochemical markers for
neurological syndromes., Diagnosis of Alzheimer's disease comprises (a) contacting in the
presence of micromolar levels of Mn cerebrospinal fluid contg. a nucleotide binding protein
with a mol. wt. of 43kd, where the protein is glutamine synthetase, with labelled ATP-GTP-
analog photoaffinity, binding reagents; (b) fractionating the sample to separate
photoaffinity-l abelled protein; (c) detecting the presence of sepd. protein, and (d)
correlating the presence of the protein to the presence of Alzheimer's disease. Reagent is
e.g. 32-P-8-azidoadenosine-5'-triphosphate. Sepn. is pref. performed by gel
electrophoresis., USE/ADVANTAGE - Diagnosis of Alzheimer's disease and other neurological
syndromes or diseases eg. ALs. Method is reliable, accurate, safe and effective.

L7: Entry 36 of 44

File: DWPI

Feb 19, 1998

DERWENT-ACC-NO: 1995-170233
DERWENT-WEEK: 199824

TITLE: Aiding the diagnosis of Alzheimer's disease - comprises detecting a disease-specific
biochemical marker macromolecule within a cerebro-spina l fluid or serum sample

ABEQ:
Diagnosis of Alzheimer's disease comprises (a) contacting in the presence of micromolar levels of
Mn cerebrospinal fluid contg. a nucleotide binding protein with a mol. wt. of 43kd, where the
protein is glutamine synthetase, with labelled ATP-GTP- analog photoaffinity, binding reagents;
(b) fractionating the sample to separate photoaffinity-l abelled protein; (c) detecting the
presence of sepd. protein, and (d) correlating the presence of the protein to the presence of
Alzheimer's disease. Reagent is e.g. 32-P-8-azidoadenosine-5'-triphosphate. Sepn. is pref.
performed by gel electrophoresis.

37. Document ID: US 6040140 A, WO 9426930 A1

L7: Entry 37 of 44

File: DWPI

Mar 21, 2000

DERWENT-ACC-NO: 1995-006818
DERWENT-WEEK: 200021

TITLE: New acute lymphocytic leukaemia gene prods. - used for the diagnosis and treatment of
leukaemia(s), partic. acute lymphoblastic or nonlymphoblastic leukaemia

PRIORITY-DATA: 1993US-0062443 (May 14, 1993), 1991US-0805093 (December 11, 1991), 1992US-0888839
(May 27, 1992), 1992US-0971094 (October 30, 1992), 1996US-0545860 (March 7, 1996)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 6040140 A	March 21, 2000	N/A	000	C12Q001/68

WO 9426930 A1
November 24, 1994
E
207
C12Q001/68

APPLICATION-DATA:
PUB-NO
APPL-DATE
APPL-NO
DESCRIPTOR
US 6040140A
December 11, 1991
1991US-0805093
CIP of
US 6040140A
May 27, 1992
1992US-0888839
CIP of
US 6040140A
October 30, 1992
1992US-0971094
CIP of
US 6040140A
May 14, 1993
1993US-0062443
CIP of
US 6040140A
April 22, 1994
1994WO-US04496
N/A
US 6040140A
March 7, 1996
1996US-0545860
N/A
WO 9426930A1
April 22, 1994
1994WO-US04496
N/A

INT-CL (IPC): A61K 39/395; A61K 48/00; C07H 21/02; C07H 21/04; C07K 15/28; C12P 19/34; C12Q 1/68; G01N 33/53; G01N 33/574

IN: CANAANI, E, CROCE, C

AB: (A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15 nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4; (ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii) the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i) the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc., USE - The prods. and methods are used for the diagnosis and treatment of human leukaemias.

(A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15 nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4; (ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii) the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i) the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc., USE - The prods. and methods are used for the diagnosis and treatment of human leukaemias.

L7: Entry 37 of 44
File: DWPI
Mar 21, 2000

DERWENT-ACC-NO: 1995-006818
DERWENT-WEEK: 200021

TITLE: New acute lymphocytic leukaemia gene prods. - used for the diagnosis and treatment of leukaemia(s), partic. acute lymphoblastic or nonlymphoblastic leukaemia

ABTX:
(A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15 nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4; (ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii) the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i) the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc.

ABEQ:
(A) A probe is claimed comprising an oligonucleotide (ON) sequence or deriv. of at least 15
nucleotides which identifies chromosome abnormalities within (i) the AF-4 gene of chromosome 4;
(ii) the AF-9 gene of chromosome 9; (iii) the AF-6 gene of chromosome 6; or (iv) the AF-17 gene
of chromosome 17. Also claimed are: (B) a monoclonal antibody (MAb) which binds to at least a
portion of (i) the chimeric ALL-1/AF-9 protein; (ii) the chimeric ALL-1/AF-6 protein; or (iii)
the chimeric ALL-1/AF-17 protein; (C) an antisense ON which binds to at least a portion of (i)
the chimeric ALL-1/AF-9 mRNA; (ii) the chimeric ALL-1/AF-6 mRNA; or (iii) the chimeric
ALL-1/AF-17 mRNA; (D) a probe which identifies chromosomal abnormalities in the ALL-1 gene, the
probe comprising B859; (E) a method of diagnosing acute lymphoblastic leukaemia (ALL) or acute
nonlymphoblastic leukaemia (ANLL) comprising (a) providing a tissue sample contg. haematopoietic
cells from a patient and (b) detecting (i) chromosomal abnormalities within the AF-4 gene of
chromosome 4, the AF-9 gene of chromosome 9, the AF-6 gene of chromosome 6 or the AF-17 gene of
chromosome 17 in genetic material from the cells or (ii) at least a portion of the chimeric
ALL-1/AF-9 protein, the chimeric ALL-1/AF-6 protein or the chimeric ALL-1/AF-17 protein; etc.

38. Document ID: US 5506120 A, WO 9206211 A, JP 04148694 A, EP 591524 A1, EP 591524 A4, JP 95108232 B2
L7: Entry 38 of 44
File: DWPI
Apr 9, 1996

DERWENT-ACC-NO: 1992-150895
DERWENT-WEEK: 199620

TITLE: High yield prodn. of peptide(s) with physiological activity - by expressing fused protein
in transfornant microorganism having peptide linked to carrier via di:peptide, then cleaving with
protease

PRIORITY-DATA: 1990JP-0271880 (October 9, 1990)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
US 5506120 A	April 9, 1996	N/A	027	C12N015/62
WO 9206211 A	April 16, 1992	J	053	N/A
JP 04148694 A	May 21, 1992	N/A	023	C12P021/06
EP 591524 A1	April 13, 1994	E	030	C12P021/06
EP 591524 A4	August 3, 1994	N/A	000	N/A
JP 95108232 B2	November 22, 1995	N/A	019	C12P021/02

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
US 5506120A	February 25, 1991	1991WO-JP00239	Cont of
US 5506120A	June 5, 1992	1992US-0853754	Cont of
US 5506120A	May 16, 1994	1994US-0243082	N/A
WO 9206211A	February 25, 1991	1991WO-JP00239	N/A
JP04148694A	October 9, 1990	1990JP-0271880	N/A
EP 591524A1	February 25, 1991	1991EP-0904654	N/A
EP 591524A1	February 25, 1991	1991WO-JP00239	N/A
EP 591524A1		WO 9206211	Based on
EP 591524A4		1991EP-0904654	N/A
JP95108232B2	October 9, 1990	1990JP-0271880	N/A
JP95108232B2		JP 4148694	Based on

INT-CL (IPC): C07K 13/00; C12N 15/09; C12N 15/62; C12P 21/02; C12P 21/06; C12R 1/12; C12P 21/02; C12R 1/125;
C12P 21/02 ; C12R 1/125; C12P 21/02; C12R 1/125

IN: YAMAMOTO, H, YAMASHITA, K, KUWATA, M

AB: Peptides and proteins are obtd. by (a) producing a fused protein consisiting of
the desired peptide or protein linked to a carrier molecule by an enzymically-cleavable
dipeptide; (b) cleaving the dipeptide by menas of a protease (which may be an aminopeptidase
or carboxypeptidase) to give the free desired protein or peptide. In (a) the fused protein
is obtd. as the prod. of culture of a transforman t microorganism and has

the structure
A-B-C or C-B-A (where A is the carrier, B the dipeptide and C the desired peptide or
protein; B is -X1-X2- where X1 is LYS, PRO, or ARG and X2 is LYS or ARG (but excepting
X1=PRO, X2=ARG) or may have a multiple structure A-(B-C)n or (C-B)n-A (where n is pref.
2-20)., The carrier A is A pref. alpha-amylase, neutral protease, alkali protease,
cellulose, beta-lactamase, beta-galactosidase, chloroamphenicol acetyltransferase, RecA,
TrpE or human interferon 2 etc. The linker dipeptide is -LYS-ARG or -ARG-ARG-. The protease
in (b) is IRCM serine protease, I, POMC converting enzyme, or a protease derived from
Saccharomyces, Kluyveromyces, Sporobolomyces, Filobasidium, Hansenula, Issatchenkia, Pichia,
Rhodosporidium or Saccharomycopsis., USE/ADVANTAGE - High yield prodn. of peptides such as
insulin, gastrin, opioid peptides, epidermal growth factor, endoserine, vasoactive
intestinal peptide (VIP) substance P, calcitonin, insulin-dependent growth factor (I or II),
gramine, motilin, vasopressin, hirudin, egurin C, serum protease inhibitor, human albumin,
clotting factors or lymphokines., A new method of producing a peptide or a protein, wherein
said method comprises expressing a recombinant DNA in a host microorganism, said DNA
encoding a fusion protein represented by the formula A-B-C(I) or C-B-A(II) where A
represents a carrier, B represents an enzymatically excisable dipeptide of the formula X1-X2
(in which X1 is Lys, Arg or Pro bound to the C-terminus of A in the case of (I) and to the
C-terminus of C in the case of (II), and X2 is Lys or Arg bound to the N-terminus of C in
the case of (I) and to the N-terminus of A in the case of (II) provided that when X1 is Pro,
X2 is Arg, which does not occur in a desired peptide or protein, and C represents the
desired peptide or protein, said host microorganism being a mutant strain showing low
protease productivity derived from a parent Bacillus subtilis strain by introduction of a
spoOA-delta677 mutant gene, wherein said parent Bacillus subtilis lacks an ability to
produce either alkaline protease or neutral protease and shows a protease activity of not
more than about 3% as compared to wild strains, and treating said fusion protein at least
with a protease capable of specifically recognizing said dipeptide represented by B and
specifically hydrolyzing a peptide bond of said dipeptide.

L7: Entry 38 of 44

File: DWPI

Apr 9, 1996

DERWENT-ACC-NO: 1992-150895
DERWENT-WEEK: 199620
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TITLE: High yield prodn. of peptide(s) with physiological activity - by expressing fused protein
in transformant microorganism having peptide linked to carrier via di:peptide, then cleaving with
protease

ABEQ:
A new method of producing a peptide or a protein, wherein said method comprises expressing a
recombinant DNA in a host microorganism, said DNA encoding a fusion protein represented by the
formula A-B-C(I) or C-B-A(II) where A represents a carrier, B represents an enzymatically
excisable dipeptide of the formula X1-X2 (in which X1 is Lys, Arg or Pro bound to the C-terminus
of A in the case of (I) and to the C-terminus of C in the case of (II), and X2 is Lys or Arg
bound to the N-terminus of C in the case of (I) and to the N-terminus of A in the case of (II)
provided that when X1 is Pro, X2 is Arg, which does not occur in a desired peptide or protein,
and C represents the desired peptide or protein, said host microorganism being a mutant strain
showing low protease productivity derived from a parent Bacillus subtilis strain by introduction
of a spoOA-delta677 mutant gene, wherein said parent Bacillus subtilis lacks an ability to
produce either alkaline protease or neutral protease and shows a protease activity of not more
than about 3% as compared to wild strains, and treating said fusion protein at least with a
protease capable of specifically recognizing said dipeptide represented by B and specifically
hydrolyzing a peptide bond of said dipeptide.

39. Document ID: WO 9101006 A, CA 2018856 A, JP 04500731 W, EP 617790 A1, US 5364796 A, EP 617790 B1, DE 69023517 E, ES 2081993 T3, JP 2574068 B2
L7: Entry 39 of 44

File: DWPI

Jan 24, 1991

DERWENT-ACC-NO: 1991-051402
DERWENT-WEEK: 199810
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TITLE: Multilayer diagnostic assay system - esp. useful for estimating sites on thyroxine binding
globulin (TBG) not occupied by thyroxine

PRIORITY-DATA: 1989US-0378062 (July 11, 1989)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
WO 9101006 A	January 24, 1991	N/A	020	N/A
CA 2018856 A	January 11, 1991	N/A	000	N/A
JP 04500731 W	February 6, 1992	N/A	006	N/A
EP 617790 A1	October 5, 1994	E	020	G01N033/68
US 5364796 A	November 15, 1994	N/A	006	G01N033/53
EP 617790 B1				

November 8, 1995
E
010
G01N033/68
DE 69023517 E
December 14, 1995
N/A
000
G01N033/68
ES 2081993 T3
March 16, 1996
N/A
000
G01N033/68
JP 2574068 B2
January 22, 1997
N/A
005
G01N033/543

APPLICATION-DATA:
PUB-NO
APPL-DATE
APPL-NO
DESCRIPTOR
JP04500731W
June 12, 1990
1990JP-0509877
N/A
EP 617790A1
June 12, 1990
1990EP-0909892
N/A
EP 617790A1
June 12, 1990
1990WO-US03313
N/A
EP 617790A1
WO 9101006
Based on
US 5364796A
July 11, 1989
1989US-0378062
N/A
EP 617790B1
June 12, 1990
1990EP-0909892
N/A
EP 617790B1
June 12, 1990
1990WO-US03313
N/A
EP 617790B1
WO 9101006
Based on
DE69023517E
June 12, 1990
1990DE-0623517
N/A
DE69023517E
June 12, 1990
1990EP-0909892
N/A
DE69023517E
June 12, 1990
1990WO-US03313
N/A
DE69023517E
EP 617790
Based on
DE69023517E
WO 9101006
Based on
ES 2081993T3
June 12, 1990
1990EP-0909892
N/A
ES 2081993T3
EP 617790
Based on
JP 2574068B2
June 12, 1990
1990JP-0509877
N/A
JP 2574068B2
June 12, 1990
1990WO-US03313
N/A
JP 2574068B2
JP 4500731
Previous Publ.
JP 2574068B2
WO 9101006
Based on

INT-CL (IPC): G01N 21/00; G01N 21/78; G01N 33/53; G01N 33/533; G01N 33/543; G01N 33/563; G01N 33/58; G01N 33/68; G01N 33/78

IN: BLACKWOOD, J J, INBAR, S, PATZKE, J V

AB: Method for assessing the available ligand binding sites on proteins comprises (a)
distributing a sample of a fluid contg a protein (I) across the surface of a multilayer
diagnostic assay element comprising (i) a light-blocking layer which is permeable to the
fluid but impermeable to (I); and (ii) a reagent layer comprising a ligand (II), which can
bind to available binding sites on (I); (b) measuring the amt of (II) which is in the
reagent layer or on (I); and (c) assessing the available ligand binding sites on (I) as a
function of the amt of (II) in the reagent layer or on (I)., USE - Assay may be used to
assess the available binding sites on receptors for hormones, on proteins eg folic binding
proteins for folic acid, or for assessing the presence of available binding sites on
endogenous antibodies which are raised against infectious diseases. The assay system is pref
used (as claimed) to provide an indirect estimate of the binding sites on TBG which are not
occupied by thyroid hormones. This reuslt, taken together with that obtd in a separate assay
for total T4 carried out with another sample of the same fluid, provides an indirect measure
of free T4 in the sample and can be used to calculate a free thyroxine index (FTI)., A
method for assessing the available ligand binding sites on proteins comprising (a)
distributing a sample of a fluid containing a protein across the surface of a multilayer
diagnostic assay element which comprises: (i) a light blocking layer which is permeable to
said fluid but impermeable to said protein; and (ii) a reagent layer comprising a ligand
which is capable of binding to available binding sites on said protein; (b) measuring the
amount of ligand which is present in said reagent layer on or said protein; and (c)
assessing the available ligand binding sites on said protein as a function of the amount of
ligand present in said reagent layer or on said protein., Assessing the available ligand
binding sites on proteins comprises (a) distributing a sample of a fluid contg. a protein
across the surface of a multilayer diagnostic assay element comprising (i) a light blocking
layer which is permeable to the fluid but impermeable to the protein, and (ii) a reagent
layer comprising a ligand which binds to available binding sites on the protein, (b)
measuring the amt. of ligand in the reagent layer or on the protein, and (c)

assessing the
available ligand binding sites on the protein as a function of the amt. of ligand in the
reagent layer or on the protein., Pref. the ligand is bound to a label comprising a
fluorescent gp. The ligand is thyroxine or triiodothyronine., USE - Used for assessing
available binding sites on proteins in biological fluids, e.g. thyroxine binding proteins in
serum or plasma samples.

L7: Entry 39 of 44

File: DWPI

Jan 24, 1991

DERWENT-ACC-NO: 1991-051402
DERWENT-WEEK: 199810

TITLE: Multilayer diagnostic assay system - esp. useful for estimating sites on thyroxine binding
globulin (TBG) not occupied by thyroxine

ABEQ:
A method for assessing the available ligand binding sites on proteins comprising (a) distributing
a sample of a fluid containing a protein across the surface of a multilayer diagnostic assay
element which comprises: (i) a light blocking layer which is permeable to said fluid but
impermeable to said protein; and (ii) a reagent layer comprising a ligand which is capable of
binding to available binding sites on said protein; (b) measuring the amount of ligand which is
present in said reagent layer on or said protein; and (c) assessing the available ligand binding
sites on said protein as a function of the amount of ligand present in said reagent layer or on
said protein.

ABEQ:
Assessing the available ligand binding sites on proteins comprises (a) distributing a sample of a
fluid contg. a protein across the surface of a multilayer diagnostic assay element comprising (i)
a light blocking layer which is permeable to the fluid but impermeable to the protein, and (ii) a
reagent layer comprising a ligand which binds to available binding sites on the protein, (b)
measuring the amt. of ligand in the reagent layer or on the protein, and (c) assessing the
available ligand binding sites on the protein as a function of the amt. of ligand in the reagent
layer or on the protein.

40. Document ID: EP 406216 A, CA 2019745 C, NO 9002823 A, CA 2019745 A, JP 03038528 A, FI 9003197 A, US 5143901 A, EP 406216 B1, US 5254532 A, DE 59003060 G, ES 2061007 T3, FI 94927 B, AT 8901551 A, AT 402153 B

L7: Entry 40 of 44

File: DWPI

Jan 2, 1991

DERWENT-ACC-NO: 1991-009510
DERWENT-WEEK: 199712

TITLE: Protein S-contg. pharmaceutical prepn. - having 50 times more protein S than native plasma
and useful in prevention of thrombosis

PRIORITY-DATA: 1989AT-0001551 (June 26, 1989)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 406216 A	January 2, 1991	N/A	000	N/A
CA 2019745 C	December 31, 1996	N/A	000	A61K038/48
NO 9002823 A	December 27, 1990	N/A	000	N/A
CA 2019745 A	December 26, 1990	N/A	000	N/A
JP 03038528 A	February 19, 1991	N/A	000	N/A
FI 9003197 A	December 27, 1990	N/A	000	N/A
US 5143901 A	September 1, 1992	N/A	005	A61K037/00
EP 406216 B1	October 13, 1993	G	008	C07K003/20
US 5254532 A	October 19, 1993	N/A	005	A61K037/00
DE 59003060 G	November 18, 1993	N/A	000	C07K003/20
ES 2061007 T3	December 1, 1994	N/A	000	C07K003/20
FI 94927 B	August 15, 1995	N/A	000	A61K038/17
AT 8901551 A	July 15, 1996	N/A	000	A61K038/36
AT 402153 B	January 15, 1997	N/A		

000

A61K038/36

APPLICATION-DATA:
PUB-NO
APPL-DATE
APPL-NO
DESCRIPTOR

EP 406216A
June 18, 1990
1990EP-0890184
N/A

CA 2019745C
June 25, 1990
1990CA-2019745
N/A

JP03038528A
June 25, 1990
1990JP-0166528
N/A

US 5143901A
June 19, 1990
1990US-0540357
N/A

EP 406216B1
June 18, 1990
1990EP-0890184
N/A

US 5254532A
June 19, 1990
1990US-0540357
Cont of

US 5254532A
February 21, 1992
1992US-0840719
N/A

US 5254532A
US 5143901
Cont of

DE59003060G
June 18, 1990
1990DE-0503060
N/A

DE59003060G
June 18, 1990
1990EP-0890184
N/A

DE59003060G
EP 406216
Based on

ES 2061007T3
June 18, 1990
1990EP-0890184
N/A

ES 2061007T3
EP 406216
Based on

FI 94927B
June 26, 1990
1990FI-0003197
N/A

FI 94927B
FI 9003197
Previous Publ.

AT 8901551A
June 26, 1989
1989AT-0001551
N/A

AT 402153B
June 26, 1989
1989AT-0001551
N/A

AT 402153B
AT 8901551
Previous Publ.

INT-CL (IPC): A61K 35/16; A61K 37/00; A61K 37/02; A61K 38/17; A61K 38/36; A61K 38/48; C07K 1/22; C07K 3/20

IN: LINNAU, Y, MOLINARI, E, PFEILER, S, SCHWARZ, H P

AB: Compsn. for treating or preventing thrombosis or thromboembolic complications has a content of protein S at least 50 times that of native plasma and is free of C4b-binding protein. Opt. it also contains activated protein C., USE/ADVANTAGE - The compsns. are used; (1) to prevent thromboembolic complications in patients with inherited or acquired protein S deficiency; (2) to treat patients with elevated levels of C4b-binding protein or (3), opt. combined with protein C, for immobilisation on the surfaces of vascular prosthesis to inhibit thrombus formation. Highly purified and conc. protein S used in the compsn. contain none of the activity-inhibiting components not orally present in plasma. (Previously notified in Week 9102), A preparation for treating and preventing thromboses and thromboembolic complications, containing human plasma protein S at a concentration of at least 1.25 mg protein S/ml and free of C4-binding protein, if desired, in combination with a content of activated protein C., Pharmaceutical compsn. comprises purified protein-S, immobilised on artificial vein surfaces. Process for preventing thrombosis comprises administration of purified protein-S (at least 50 times that in natural plasma), and opt. activated protein-C, immobilised on artificial vein surfaces. Protein-S is purified by polyclonal and monoclonal antibody affinity chromatography, and is not contaminated with C4-binding protein., USE - The prods. are therapeutics and prophylactics for thrombotic and thromboembolic conditions., Process for the prophylaxis and therapy of thromboembolic complications in patients with congenital or acquired protein-S deficiency comprises admin. of a compsn. contg. protein-S (at least 50 times the concn. normally present in natural plasma), and pref. also activated protein-C, dispersed with the usual pharmaceutical carriers and opt. additives. The protein-S is previously purified from C4-b binding protein contaminant by polyclonal or monoclonal affinity chromatography., USE - The prods. are valuable anti-thrombotic agents avoiding haemorrhages as side effects.

L7: Entry 40 of 44

File: DWPI

Jan 2, 1991

DERWENT-ACC-NO: 1991-009510
DERWENT-WEEK: 199712

TITLE: Protein S-contg. pharmaceutical prepn. - having 50 times more protein S than native plasma and useful in prevention of thrombosis

ABTX:
USE/ADVANTAGE - The compsns. are used: (1) to prevent thromboembolic complications in patients with inherited or acquired protein S deficiency; (2) to treat patients with elevated levels of C4b-binding protein or (3), opt. combined with protein C, for immobilisation on the surfaces of vascular prosthesis to inhibit thrombus formation. Highly purified and conc. protein S used in the compsn. contain none of the activity-inhibiting components not orally present in plasma.

(Previously notified in Week 9102)

ABEQ:
A preparation for treating and preventing thromboses and thromboembolic complications, containing
human plasma protein S at a concentration of at least 1.25 mg protein S/ml and free of C4-binding
protein, if desired, in combination with a content of activated protein C.

41. Document ID: EP 356836 A, DE 68915226 E, EP 356836 B1, ES 2056164 T3, JP 03086900 A, JP 95020997 B2, US 5043425 A
L7: Entry 41 of 44
File: DWPI
Mar 7, 1990

DERWENT-ACC-NO: 1990-068657
DERWENT-WEEK: 199010

TITLE: New thrombin-binding substances - capable of promoting thrombin catalysed activation of
protein C and prolonging clotting time, used to treat thrombosis

PRIORITY-DATA: 1989JP-0202027 (August 3, 1989), 1988JP-0214139 (August 29, 1988), 1989JP-0116471
(May 10, 1989)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 356836 A	March 7, 1990	G	013	N/A
DE 68915226 E	June 16, 1994	N/A	000	A61K035/22
EP 356836 B1	May 11, 1994	E	016	A61K035/22
ES 2056164 T3	October 1, 1994	N/A	000	A61K035/22
JP 03086900 A	April 11, 1991	N/A	000	N/A
JP 95020997 B2	March 8, 1995	N/A	006	C07K014/47
US 5043425 A	August 27, 1991	N/A	000	N/A

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 356836A	August 18, 1989	1989EP-0115272	N/A
DE68915226E	August 18, 1989	1989DE-0615226	N/A
DE68915226E	August 18, 1989	1989EP-0115272	N/A
DE68915226E		EP 356836	Based on
EP 356836B1	August 18, 1989	1989EP-0115272	N/A
ES 2056164T3	August 18, 1989	1989EP-0115272	N/A
ES 2056164T3		EP 356836	Based on
JP03086900A	August 3, 1989	1989JP-0202027	N/A
JP95020997B2	August 3, 1989	1989JP-0202027	N/A
JP95020997B2		JP 3086900	Based on
US 5043425A	August 16, 1989	1989US-0394715	N/A

INT-CL (IPC): A61K 35/22; A61K 38/00; C07K 1/00; C07K 1/16; C07K 14/47; C12P 21/00; C12P 21/00; C12R 1/91

IN: AOKI, N, KIMURA, S, SHIRATSUCHI, M, SHIRATSUCH, M

AB: Thrombin binding substances are claimed having the following characteristi cs:
(A) (a) mol. wt.% 90,000-92,000 under reducing conditions and 55,000-58,000 under
non-reducing conditions; (b) isoelectric point: pH 6-6.8; (c) affinity: has strong affinity
to thrombin, (d) activity: (i) capable of promoting the thrombin catalysed activation of
protein C, (ii) prolongs clotting time and (e) stability: stable to denaturing agents
(sodium dodcylsulphate and urea); (B) (a) mol. wt.98,000-105,000 under reducing conditions
and 60,000-65,000 under non-reducing conditions; (b) isoelectric point: pH 5.8-6.5; (c)
affinity: strong affinity to thrombin; (d) activity: (i) capable of promoting the thrombin
catalysed activation of protein C, (ii) prolongs clotting time and (e) stability: stable to
denaturing agents (sodium dodecylsulphate and urea)., USE/ADVANTAGE - Thrombin-bonding
substances are high mol. wt. substances with calcium-binding sites so show more natural
pharmaceutical effect than thrombin-bonding substances with smaller mol. wt. Used for
treating thrombosis involving anticoagulation and fibrinolytic systems

which control blood
coagulation., A thrombin-binding substance having the following characteristics: (a)
molecular weight: 90,000-92,000 under reduced conditions 55,000-58,000 under unreduced
conditions (b) isoelectric point: pH 6.0-6.8 (c) affinity: has strong affinity to thrombin
(d) activity: (1) capable of promoting the thrombin catalysed activation of protein C (2)
prolongs clotting time; and (e) stability: stable to denaturing agents (sodium dodecyl
sulfate and urea)., A purified thrombin-binding substance having the following
characteristics : (a) molecular weight as determined by SDS-PAGE: 90,000-92,000 under
reduced conditions 55,000-58,000 under unreduced conditions (b) isoelectric point: pH
6.0-6.8 (c) affinity: has strong affinity to thrombin (d) activity: (1) capable of promoting
the thrombin catalysed activation of protein C (2) prolongs clotting time; and (e)
stability: stable to denaturing agents (sodium dodecylsulfate and urea) (f) amino acid
composition: Aspartic acid 9.59, Threonine 4.45, Serine 5.42, Glutamic acid 11.29, Proline
8.86, Glycine 10.26, Alanine 10.88, 1/2 Cystine 8.27, Valine 5.54, Methionine 0.78,
Isoleucine 2.84, Leucine 7.15, Tyrosine 2.25 and Phenylalanine 3.50., (-pp)

L7: Entry 41 of 44

File: DWPI

Mar 7, 1990

DERWENT-ACC-NO: 1990-068657
DERWENT-WEEK: 199010

TITLE: New thrombin-binding substances - capable of promoting thrombin catalysed activation of
protein C and prolonging clotting time, used to treat thrombosis

42. Document ID: EP 354504 A, AU 8939372 A, DK 8903887 A, FI 8903724 A, JP 02046296 A, NO 8903196 A, PT 91391 A

L7: Entry 42 of 44

File: DWPI

Feb 14, 1990

DERWENT-ACC-NO: 1990-046218
DERWENT-WEEK: 199007

TITLE: Human protein C deriv. - having Gla domain replaced by the bovine Gla to increase calcium
binding activity and improve activation

PRIORITY-DATA: 1988JP-0197144 (August 9, 1988)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 354504 A	February 14, 1990	E	017	N/A
AU 8939372 A	April 12, 1990	N/A	000	N/A
DK 8903887 A	February 10, 1990	N/A	000	N/A
FI 8903724 A	February 10, 1990	N/A	000	N/A
JP 02046296 A	February 15, 1990	N/A	000	N/A
NO 8903196 A	March 5, 1990	N/A	000	N/A
PT 91391 A	March 8, 1990	N/A	000	N/A

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 354504A	August 5, 1989	1989EP-0114505	N/A
JP02046296A	August 9, 1988	1988JP-0197144	N/A

INT-CL (IPC): A61K 37/54; C07H 21/04; C07K 13/00; C07K 15/06; C12N 5/00; C12N 9/64; C12N 15/57; C12P 19/00; C12P 21/02

IN: HASHIMOTO, T, TAKAHASHI, M

AB: (A) A deriv. of human protein C is claimed characterised in that its amino
terminal region having gamma-carboxylated glutamic acid residues (Gla domain) is replaced by
the Gla domain of bovine protein C or by an equivalent of this bovine protein sequence with
respect to its calcium binding activity and/or its enhanced protein C activity. (B) also
claimed are DNA coding for the protein of (A), a gene structure contg. the DNA and a host
cell contg. the gene structure., USE/ADVANTAGE - The hybrid proteins have an increased
number of glutamic residues (from 9 to 11). Through th increase of the number of
gamma-carboxylation sites, enhanced calcium binding activity of protein C and improved
activation of protein C, is obtd. The activated protein C inhibits blood coagulation or
accelerates blood fibrinolysis and is used for treating blood coagulation.

L7: Entry 42 of 44

File: DWPI

Feb 14, 1990

DERWENT-ACC-NO: 1990-046218
DERWENT-WEEK: 199007

TITLE: Human protein C deriv. - having Gla domain replaced by the bovine Gla to increase calcium
binding activity and improve activation

ABTX:
USE/ADVANTAGE - The hybrid proteins have an increased number of glutamic residues (from 9 to 11).
Through th increase of the number of gamma-carboxylation sites, enhanced calcium binding activity
of protein C and improved activation of protein C, is obtd. The activated protein C inhibits
blood coagulation or accelerates blood fibrinolysis and is used for treating blood coagulation.

43. Document ID: EP 253331 A, DE 3750664 G, EP 253331 B1, ES 2065318 T3, JP 63030423 A, JP 63146898 A, US 5047503 A
L7: Entry 43 of 44
File: DWPI
Jan 20, 1988

DERWENT-ACC-NO: 1988-015706
DERWENT-WEEK: 198803

TITLE: Two new thrombin binding proteins from human urine - promoting activation of protein C and
useful in treatment of thrombosis

PRIORITY-DATA: 1986JP-0172626 (July 22, 1986), 1986JP-0166084 (July 15, 1986), 1987JP-0168428
(July 6, 1987)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 253331 A	January 20, 1988	E	027	N/A
DE 3750664 G	November 24, 1994	N/A	000	C07K015/06
EP 253331 B1	October 19, 1994	E	009	C07K015/06
ES 2065318 T3	February 16, 1995	N/A	000	C07K015/06
JP 63030423 A	February 9, 1988	N/A	000	N/A
JP 63146898 A	June 18, 1988	N/A	000	N/A
US 5047503 A	September 10, 1991	N/A	000	N/A

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 253331A	July 10, 1987	1987EP-0110005	N/A
DE 3750664G	July 10, 1987	1987DE-3750664	N/A
DE 3750664G	July 10, 1987	1987EP-0110005	N/A
DE 3750664G		EP 253331	Based on
EP 253331B1	July 10, 1987	1987EP-0110005	N/A
ES 2065318T3	July 10, 1987	1987EP-0110005	N/A
ES 2065318T3		EP 253331	Based on
JP63030423A	July 22, 1986	1986JP-0172626	N/A
JP63146898A	July 6, 1987	1987JP-0168428	N/A
US 5047503A	July 10, 1987	1987US-0072051	N/A

INT-CL (IPC): A61K 35/22; C07K 3/12; C07K 15/06; C12N 5/00; C12N 15/00; C12P 21/00

IN: AOKI, N, KIMURA, S, SHIRATSUCHI, M, KLMURA, S, SHIRATSUCH, M

AB: Two new thrombin-binding substances, (I) and (II), derived from human urine have
the following characteristics: (1) mol. wt., for (I) 40500-52500 and 29000-49000 by Na
dodecylsulphate-polyacrylamide gel electrophoresis (SDS-PAGE) under reducing and
non-reducing conditions, respectively; for (II) 32000-48000 and 21000-41000; (2) isoelectric
point: for (I) 5-5.3, for (II) 4.9-5.7; (3) for both cpds., strong affinity to thrombin;
promotion of thrombin-catalysed activated of protein C; prolongation of clotting time and
stability towards denaturing agents such as urea and SDS.,
USE/ADVANTAGE - (I) and (II) act
as fibrinolytic accelerators or anticoagulants, so are useful for treating thrombosis and
similar conditions. They are prepd. more easily than known placental

thrombin-bind ing
substances, and can be isolated from urine after recovery of other useful prods. such as
urokinase., A process for preparing a thrombin-binding substance having the following
characteristics: (a) molecular weight: 40,000 +/- 8,000 in reduced condition by SDS PAGE
31,000 +/- 10,000 in unreduced condition by SDS PAGE (b) isoelectric point: pH 4.9-5.7 (c)
affinity: strong affinity to thrombin (d) activity: (1) capable of promoting the thrombin
catalysed activation of protein C (2) prolongs clotting time; and (e) stability; stable to
denaturing agents (urea and sodium dodecylsulfate), which comprises fractionating human
urine by ion-exchange chromatography, affinity chromatography using a thrombin-bound
carrier, immune adsorption column chromatography, gel filtration, and/or molecular-weight
fractionation., A new thrombin-binding substance is prepd. by successively subjecting human
urine to ion exchange chromatography, affinity chromatography on a column of a
thrombin-bound carrier, gel-filtration and molecular wt. fractionation. Pref. benzamidine
HCl or aprotinin is added to the urine before ion exchange chromatography. The urine may be
subjected to immune absorption column chromatography using as packing a monoclonal antibody
specific to the thrombin-binding substance bound on an insol. carrier, followed by ion
exchange. Two thrombin-bindin g substances are obtd. (a) with MW 46500 +/-6000 in reduced
condition by SDS PAGE and 39000 +/- 10000 in unreduced condition; isoelectric pt. pH
5.0-5.3; strong affinity to thrombin; stable to denaturing agents (urea or Na
dodecylsulphoate). (b) has MW 40000 +/- 8000 in reduced conditiona nd 31000 +/- 10000 in
unreduced condition; isoelectric pt. pH 4.9-5.7; and other characteristics as (a). USE.-
Both cpds. are capable of promoting the thrombin-catalysed activation of protein C and
prolonging clotting time. They are also fibrinolytic accelerators and anticoagulants used to
control coagulation of blood., (7pp)

L7: Entry 43 of 44
File: DWPI
Jan 20, 1988

DERWENT-ACC-NO: 1988-015706
DERWENT-WEEK: 198803

TITLE: Two new thrombin binding proteins from human urine - promoting activation of protein C and
useful in treatment of thrombosis< /td>

44. Document ID: EP 155852 A, DE 3577399 G, EP 155852 B, JP 60199819 A, JP 93045600 B, US 4638050 A
L7: Entry 44 of 44
File: DWPI
Sep 25, 1985

DERWENT-ACC-NO: 1985-238346
DERWENT-WEEK: 198539

TITLE: Thrombin binding substance - obtd. from human placenta used as thrombolyti c or
anticoagulant

PRIORITY-DATA: 1984JP-0055792 (March 23, 1984)

PATENT-FAMILY:

PUB-NO	PUB-DATE	LANGUAGE	PAGES	MAIN-IPC
EP 155852 A	September 25, 1985	E	016	N/A
DE 3577399 G	June 7, 1990	N/A	000	N/A
EP 155852 B	May 2, 1990	N/A	000	N/A
JP 60199819 A	October 9, 1985	N/A	000	N/A
JP 93045600 B	July 9, 1993	N/A	005	C07K015/06
US 4638050 A	January 20, 1987	N/A	000	N/A

APPLICATION-DATA:

PUB-NO	APPL-DATE	APPL-NO	DESCRIPTOR
EP 155852A	March 21, 1985	1985EP-0301959	N/A
JP60199819A	March 23, 1984	1984JP-0055792	N/A
JP93045600B	March 23, 1984	1984JP-0055792	N/A
JP93045600B		JP60199819	Based on
US 4638050A	March 20, 1985	1985US-0713821	N/A

INT-CL (IPC): A61K 35/50; A61K 37/04; C07K 3/02; C07K 15/06

IN: AOKI, N, KUROSAWA, S

AB: A thrombin-binding substance (I) derived from human tissue has the following
props. (a) mol.wt. 88,000+/-20,000 in the reduced condition and 71,000+/-20,000 in the

unreduced condition, (c) isoelectric point pH 4.2+/-0.5, (c) affinity:strong for thrombin,
(d) capable of promoting the thrombin-catalysed activation of protein C and prolonging
clotting time and (e) stability:stable over a pH range of 2-10 and stable to denaturing
agents (sodium dodecylsulphate and urea) and to a pepsin treatment., USE - (I) is useful as
a thrombolytic agent or an anticoagulating agent., A thrombin-binding substance effective
when bonded with thrombin to enhance the activation of protein C, derived from human tissue
and having the following characteristics; (a) molecular wt.; 88,000 +/- 20,000 in the
reduced condition and 71,000 +/- 20,000 in the unreduced condition; (b) isoelectric point;
pH 4.2 +/- 0.5; (c) affinity; strong for thrombin; (d) activities; capable of promoting the
thrombin-catalysed activation of protein C and prolonging clotting time; and (e) stability;
stable over a pH range of 2-10 and stable to denaturing agents (dodecylsulphate and urea)
and to a pepsine treatment. (8pp), Thrombin binding substance (TBS) is obtd. by (a)
extracting human tissue, esp. the placenta, with a buffer contg. a nonionic surfactant and
(b) isolating the pure TBS from the extract by diisopropylphosphoro thrombin affinity
chromatography and/or gel filtration and pref. (c) eluting the TBS with a buffer contg.
NaCl, EDTA, benzamidine HCl and a nonionic surfactant., The TBS (a) has a mol.wt.
68,000-108,000 in reduced form and 51,000-91,000 in unreduced form, (b) has an isoelectric
point pH 3.7-4.7, (c) has a strong affinity for thrombin, (d) is able to prevent the
thrombin catalysed activation of protein C and prolongs clotting time and (e) is stable at
pH 2-10, stable to denaturing agents and pepsin treatment., USE/ADVANTAGE - As thrombolytic
agent or anticoagulating agent; the agent can be obtd. in pure form. B(6pp)t

L7: Entry 44 of 44

File: DWPI

Sep 25, 1985

DERWENT-ACC-NO: 1985-238346
DERWENT-WEEK: 198539

TITLE: Thrombin binding substance - obtd. from human placenta used as thrombolyti c or
anticoagulant

ABEQ:
A thrombin-binding substance effective when bonded with thrombin to enhance the activation of
protein C, derived from human tissue and having the following characteristics; (a) molecular wt.;
88,000 +/- 20,000 in the reduced condition and 71,000 +/- 20,000 in the unreduced condition; (b)
isoelectric point; pH 4.2 +/- 0.5; (c) affinity; strong for thrombin; (d) activities; capable of
promoting the thrombin-catalysed activation of protein C and prolonging clotting time; and (e)
stability; stable over a pH range of 2-10 and stable to denaturing agents (dodecylsulphate and
urea) and to a pepsine treatment. (8pp)

09/139425
A11#14

```
    Set  Items  Description
    ---  -----  -----------
? s protein(w)c

      2938916  PROTEIN
      2178289  C
    S1  27187  PROTEIN(W)C
? s epcr

    S2     96  EPCR
? s s1(w)receptor

       27187  S1
     1321224  RECEPTOR
    S3    134  S1(W)RECEPTOR
? s s2 or s3

         96  S2
        134  S3
    S4    147  S2 OR S3
? s antibod?

Processing
    S5 1478948  ANTIBOD?
? s treat? or diagnos?

Processing
Processing
     4385448  TREAT?
     3971290  DIAGNOS?
    S6 7599752  TREAT? OR DIAGNOS?
? s s4 and s5

        147  S4
     1478948  S5
    S7     26  S4 AND S5
? s s1 and s5

       27187  S1
     1478948  S5
    S8   3969  S1 AND S5
? s bind? or bound

     1571243  BIND?
      401937  BOUND
    S9 1759385  BIND? OR BOUND
? rd

>>>A maximum of 5000 items can be processed.
<------User Break------>
!


? ds


Set    Items  Description
S1     27187  PROTEIN(W)C
S2        96  EPCR
S3       134  S1(W)RECEPTOR
S4       147  S2 OR S3
S5   1478948  ANTIBOD?
S6   7599752  TREAT? OR DIAGNOS?
S7        26  S4 AND S5
S8      3969  S1 AND S5
S9   1759385  BIND? OR BOUND
? s s1(n5)s9

       27187  S1
     1759385  S9
   S10   2429  S1(N5)S9
? s s10 and s6

        2429  S10
     7599752  S6
   S11    423  S10 AND S6
? s s4 and s9

        147  S4
     1759385  S9
   S12     76  S4 AND S9
? s s7 or s12

         26  S7
         76  S12
   S13     78  S7 OR S12
? rd

...examined 50 records  (50)
...completed examining records
   S14     39  RD (unique items)
? s s14 and py<1998

Processing
Processing
         39  S14
   28044798  PY<1998
   S15     14  S14 AND PY<1998
? t s15/3,ab/1-14


 15/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)
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11279552  BIOSIS NO.: 199800060884
Specific %%%binding%%% of activated protein C (APC) to vascular smooth
 muscle cells is not due to the endothelial receptor (%%%EPCR%%%).
AUTHOR: O'Regan D J(a); Brennand D(a); Esmon C T; Goodwin C A(a);
Kakkar V
 V(a); Scully M F(a)
AUTHOR ADDRESS: (a)Thrombosis Res. Inst., Emmanuel Kaye Build.,
Manresa
 Rd., London SW3 6LR**UK
JOURNAL: Blood  90 (10 SUPPL. 1 PART 2):p78B-79B Nov. 15,
%%%1997%%%
CONFERENCE/MEETING: Thirty-ninth Annual Meeting of the American
Society of
Hematology  San Diego, California, USA  December 5-9, 1997
SPONSOR: The American Society of Hematology
ISSN: 0006-4971
RECORD TYPE: Citation
LANGUAGE: English
1997


 15/3,AB/2     (Item 2 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)
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11174614  BIOSIS NO.: 199799795759
The interaction between the endothelial cell %%%protein%%%
%%%C%%%
 %%%receptor%%% and protein C is dictated by the
gamma-carboxyglutamic
 acid domain of protein C.
AUTHOR: Regan Lisa M; Mollica Jeffery S; Rezaie Alireza R; Esmon
Charles T
 (a)
AUTHOR ADDRESS: (a)Cardiovasc. Biol. Res. Program, Oklahoma Med.
Res.
 Foundation, 825 N. E. 13th St., Oklahoma City**USA
JOURNAL: Journal of Biological Chemistry  272 (42):p26279-26284
%%%1997%%%
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%% (
 %%%EPCR%%%) %%%binds%%% to both protein C and activated
protein C (APC)
 with similar affinity. Removal of the Gla domain of protein C results in
 the loss of most of the %%%binding%%% affinity. This observation is
 compatible with at least two models: 1) the Gla domain of protein C
 interacts with phospholipid on cell surfaces to stabilize interaction
```

with %%%EPCR%%% or 2) the Gla domain of protein C makes specific protein-protein interactions with %%%EPCR%%%. The latter model predicts that chimeric proteins containing the protein C Gla domain should interact with %%%EPCR%%%. To test this, we constructed a prothrombin chimera in which the Gla domain and aromatic stack of prothrombin were replaced with the corresponding region of protein C. The 125I-labeled chimera (K-d = 176 nM) and 125I-APC (K-d = 65 nN) both %%%bound%%% specifically to 293 cells stably transfected with %%%EPCR%%%, but both %%%bound%%% poorly to sham-transfected cells. The chimera also blocked APC %%%binding%%% to %%%EPCR%%%-transfected cells in a dose-dependent fashion (K-i apprxeq 139 nM) similarly to protein C (K-i apprxeq 75 nM). Chimera %%%binding%%% to %%%EPCR%%%-transfected cells was blocked by soluble %%%EPCR%%%, demonstrating direct protein-protein interaction between the chimera and %%%EPCR%%%. Consistent with this conclusion, the isolated Gla domain of protein C -blocked APC %%%binding%%% to %%%EPCR%%% -transfected cells (IC-50 = 2 mu-M). No inhibition was observed with the isolated prothrombin Gla domain. A protein C chimera with the prothrombin Gla domain and aromatic stack failed to %%%bind%%% to %%%EPCR%%% detectably. These data suggest that the Gla domain of protein C is responsible for much of the %%%binding%%% energy and specificity of the protein C-%%%EPCR%%% interaction.

%%%1997%%%

15/3,AB/3 (Item 3 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

11064593 BIOSIS NO.: 199799685738
Identification of functional endothelial %%%protein%%% %%%C%%% %%%receptor%%% in human plasma.
AUTHOR: Kurosawa Shinichiro; Stearns-Kurosawa Deborah J; Hidari Noriko; Esmon Charles T(a)
AUTHOR ADDRESS: (a)825 N.E. 13th St., Oklahoma City, OK 73104**USA
JOURNAL: Journal of Clinical Investigation 100 (2):p411-418 %%%1997%%%
ISSN: 0021-9738
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (%%%EPCR%%%) %%%binds%%% protein C and facilitates activation by the thrombin-thrombomodulin complex. %%%EPCR%%% also %%%binds%%% activated protein C (APC) and inhibits APC anticoagulant activity. In this study, we detected a soluble form of %%%EPCR%%% in normal human plasma. Plasma %%%EPCR%%% appears to be apprx 43,000 D, and circulates at apprx 100 ng/ml (98.4+-27.8 ng/ml, n = 22). Plasma %%%EPCR%%% was purified from human citrated plasma using ion exchange, immunoaffinity, and protein C affinity chromatography. Flow cytometry experiments demonstrated that plasma %%%EPCR%%% %%%bound%%% APC with an affinity similar to that previously determined for recombinant soluble %%%EPCR%%% (K-dapp = 30 nM). Furthermore, plasma %%%EPCR%%% inhibited both protein C activation on an endothelial cell line and APC anticoagulant activity in a one-stage Factor Xa clotting assay. The physiological function of plasma %%%EPCR%%% is uncertain, but if the local concentrations are sufficiently high, particularly in disease states, the present data suggest that the soluble plasma %%%EPCR%%% could attenuate the membrane-%%%bound%%% %%%EPCR%%% augmentation of protein C activation and the anticoagulant function of APC.

%%%1997%%%

15/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10684157 BIOSIS NO.: 199799305302
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% participates in protein C activation.
AUTHOR: Kurosawa Shinichiro(a); Fukudome Kenji; Stearns-Kurosawa Debbie; Mollica Jeff; Ferrell Gary; Hidari Noriko; Esmon Charles T
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Fdn., Oklahoma City, OK**USA
JOURNAL: Circulation 94 (8 SUPPL.):p1694 %%%1996%%%
CONFERENCE/MEETING: 69th Scientific Sessions of the American Heart Association New Orleans, Louisiana, USA November 10-13, 1996
ISSN: 0009-7322
RECORD TYPE: Citation
LANGUAGE: English
1996

15/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10574195 BIOSIS NO.: 199699195340
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% augments protein C activation by the thrombin-thrombomodulin complex.
AUTHOR: Stearns-Kurosawa Deborah J; Kurosawa Shinichiro; Mollica Jeffery S; Ferrell Gary L; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst. Res. Lab., Acree-Woodworth Res. Building, 820 NE 15, Room A205, Oklahom**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 93 (19):p10212-10216 %%%1996%%%
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Protein C activation on the surface of the endothelium is critical to the negative regulation of blood coagulation. We now demonstrate that monoclonal %%%antibodies%%% that block protein C %%%binding%%% to the endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% (%%%EPCR%%%) reduce protein C activation rates by the thrombin-thrombomodulin complex on endothelium, but that %%%antibodies%%% that %%%bind%%% to %%%EPCR%%% without blocking protein C %%%binding%%% have no effect. The kinetic result of blocking the %%%EPCR%%%-protein C interaction is an increased apparent K-m for the activation without altering the affinity of thrombin for thrombomodulin. Activation rates of the protein C derivative lacking the gamma-carboxyglutamic acid domain, which is required for %%%binding%%% to %%%EPCR%%%, are not altered by the anti-%%%EPCR%%% %%%antibodies%%%. These data indicate that the protein C activation complex involves protein C, thrombin, thrombomodulin, and %%%EPCR%%%. These observations open new questions about the control of coagulation reactions on vascular endothelium.

%%%1996%%%

15/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10478349 BIOSIS NO.: 199699099494
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%%: Cell surface
expression and direct ligand %%%binding%%% by the soluble receptor.
AUTHOR: Fukudome Kenji; Kurosawa Shinichiro; Stearns-Kurosawa Deborah J; He
Xuhua; Rezaie Alireza R; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Foundation, Cardiovascular Biol.
Res., 825 N.E. 13th St., Oklahoma City, OK 7**USA
JOURNAL: Journal of Biological Chemistry 271 (29):p17491-17498 %%%1996%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Expression of the endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%% (%%%EPCR%%%) gene in mammalian cells imparts the capacity
to %%%bind%%% activated protein C (APC) or protein C. Immunochemical
analysis of CCD41, apparently the murine homologue of %%%EPCR%%%, suggested centrosomal localization, raising questions about the location of the %%%EPCR%%% gene product and its role in protein C %%%binding%%%.
In this study, we express a soluble form of %%%EPCR%%%, demonstrate %%%EPCR%%% expression on the cell surface, and direct %%%binding%%%
between soluble %%%EPCR%%% and protein C/APC. Affinity purified polyclonal and a monoclonal %%%antibody%%% against %%%EPCR%%% %%%bound%%%
to the cell surface of %%%EPCR%%%-transfected cells but not to control cells. A 49-kDa protein, a mass similar to soluble %%%EPCR%%%, was immunoprecipitated from the cell surface of endothelium and cells transfected with human %%%EPCR%%% but not from control cells. The FLAG
%%%antibody%%% and APC %%%bound%%% to cells expressing an %%%EPCR%%%
construct containing the FLAG epitope located in a putative extracellular domain, whereas an %%%EPCR%%% construct truncated just before the putative transmembrane domain produced only soluble %%%EPCR%%% antigen.
Soluble %%%EPCR%%% inhibited APC %%%binding%%% to %%%EPCR%%% expressing
cells in a concentration-dependent fashion, K-d(app) = 29 nM and %%%bound%%% to immobilized protein C in a Ca-2+-dependent fashion. Thus,
%%%EPCR%%% is a type I transmembrane protein that %%%binds%%% directly to
APC.

%%%1996%%%

15/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10477211 BIOSIS NO.: 199699098356
The endothelial cell %%%protein%%% %%%C%%% %%%receptor%%%: Inhibition of
activated protein C anticoagulant function without modulation of reaction with proteinase inhibitors.
AUTHOR: Regan Lisa M; Stearns-Kurosawa Deborah J; Kurosawa Shinichiro;
Mollica Jeff; Fukudome Kenji; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Oklahoma Med. Res. Foundation, Cardiovascular Biol.
Res., 825 N.E. 13th St., Oklahoma City, OK 7**USA
JOURNAL: Journal of Biological Chemistry 271 (29):p17499-17503 %%%1996%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A soluble form of the endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%% (%%%EPCR%%%) was analyzed for the ability to modulate the
functional properties of protein C and activated protein C (APC). In a plasma clotting system initiated with factor Xa, %%%EPCR%%% blocked the
anticoagulant activity of APC in a dose-dependent fashion. %%%EPCR%%% had
no influence on clotting in the absence of APC. Consistent with the plasma results, %%%EPCR%%% slowed the proteolytic inactivation of factor
Va by slowing both of the key proteolytic cleavages in the heavy chain of factor Va. %%%EPCR%%% did not prevent protein C activation by the soluble
thrombinthrombomodulin complex, did not alter the inactivation of APC by alpha-1-antitrypsin or protein C inhibitor, and did not influence the kinetics of peptide paranitroanilide substrate cleavage significantly. We conclude that %%%EPCR%%% %%%binds%%% to an exosite on APC that
selectively modulates the enzyme specificity in a manner reminiscent of the influence of thrombomodulin on thrombin.

%%%1996%%%

15/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10288691 BIOSIS NO.: 199698743609
The Gla-26 residue of protein C is required for the %%%binding%%% of protein C to thrombomodulin and endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%%, but not protein S and factor Va.
AUTHOR: Nishioka Junji; Ido Masaru; Hayashi Tatsuya; Suzuki Koji(a)
AUTHOR ADDRESS: (a)Dep. Mol. Pathobiol., Mie Univ. Sch. Med., Tsu-city, Mie
514**Japan
JOURNAL: Thrombosis and Haemostasis 75 (2):p275-282 %%%1996%%%
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A functionally defective protein C (PC)-Mie, detected in the plasma of a patient with hereditary thrombophilia, has Lys substituted for gamma-carboxyglutamic acid (Gla)-26 residue. The activation rate of PC-Mie by Protac or thrombin in the absence of Ca-2+ and that by thrombin with native thrombomodulin (TM), recombinant soluble truncated TM or on cultured endothelial cells in the presence of Ca-2+ were all apparently lower than that of normal PC. The anticoagulant activity of Protac-activated PC (APC)-Mie on the plasma clotting time and the rate of inactivation of factor Va by APC-Mie in the presence of phospholipids were lower than those seen with normal APC. APC-Mie and normal APC %%%bound%%% equally to protein S and to biotinyl-factor Va. However, neither PC-Mie nor APC-Mie %%%bound%%% to phospholipids and to cultured
human endothelial cells. It was similar to that observed with Gla-domainless PC/APC, but different from that seen with normal PC/APC. These results suggest that Gla-26-dependent conformation is required for the %%%binding%%% of PC/APC to phospholipids, TM and the surface of endothelial cell PC/APC receptor, but not to protein S and factor Va.

%%%1996%%%

15/3,AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

09765091 BIOSIS NO.: 199598220009
Molecular cloning and expression of murine and bovine endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%%

(%%%EPCR%%%):
The structural and functional conservation in human, bovine and murine %%%EPCR%%%.
AUTHOR: Fukudome Kenji; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma Med. Res. Found., 825
NE 13, Oklahoma City, OK 73104**USA
JOURNAL: Journal of Biological Chemistry 270 (10):p5571-5577 %%%1995%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Recently, we identified and cloned a human endothelial cell protein C/activated %%%protein%%% %%%C%%% %%%receptor%%% (%%%EPCR%%%).
%%%EPCR%%% was predicted to be a type 1 transmembrane glycoprotein and a
novel member of the CD1/major histocompatibility complex superfamily with
28% identity with CD1d. Even greater homology (62% identity) was detected
with the murine protein, CCD41, which was previously characterized as a centrosome-associated, cell cycle-dependent protein. This raised the possibility that CCD41 was the murine homologue of %%%EPCR%%%. To address
this possibility, to better understand structure-function relationships, and to facilitate physiological experiments on %%%EPCR%%% function, we
cloned and sequenced murine and bovine %%%EPCR%%% from endothelial cell
cDNA libraries. The nucleotide sequence of murine %%%EPCR%%% and CCD41
exhibited five differences corresponding to one base change, three single-base insertions, and one base deletion in the protein coding region. As a result, the predicted structures of %%%EPCR%%% and CCD41
differed in their amino and carboxyl termini but were identical in the central portion of the coding sequence. Based on comparison of the murine, bovine, and human %%%EPCR%%% sequences and the regions where
discrepancies between murine %%%EPCR%%% and CCD41 were detected, we
believe that CCD41 is probably identical to murine %%%EPCR%%% and that
the reported sequence differences are likely the result of compression on the sequencing gel. Compared with human %%%EPCR%%%, the murine and bovine
sequences were 69 and 73% identical, respectively, and 57% of the residues were identical between all three species. Both bovine and murine %%%EPCR%%% could %%%bind%%% human activated protein C when the cDNA
clones were transfected into 293T cells. Like human %%%EPCR%%%, of the
cell lines tested, the murine %%%EPCR%%% message was restricted to endothelium. Cloning of the murine and bovine homologue of %%%EPCR%%%
will facilitate in vivo and in vitro studies of the role of %%%EPCR%%% in the protein C pathway.

%%%1995%%%

15/3,AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09545786 BIOSIS NO.: 199598000704
Identification, Cloning, and Regulation of a Novel Endothelial Cell Protein C/Activated %%%Protein%%% %%%C%%% %%%Receptor%%%.
AUTHOR: Fukudome Kenji; Esmon Charles T(a)
AUTHOR ADDRESS: (a)Howard Hughes Med. Inst., Oklahoma Med. Res. Foundation,
825 NE 13, Oklahoma City, OK 73104**USA
JOURNAL: Journal of Biological Chemistry 269 (42):p26486-26491 %%%1994%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Human protein C and activated protein C are shown to %%%bind%%%
to endothelium specifically, selectively, and saturably (K-d = 30 nM, 7000 sites per cell) in a Ca-2+-dependent fashion. Expression cloning revealed a 1.3-kilobase pair cDNA that coded for a novel type I transmembrane glycoprotein capable of %%%binding%%% protein C. This protein appears to be a member of the CD1/major histocompatibility complex superfamily. Like thrombomodulin, the receptor involved in protein C activation, the endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% function and message are both down-regulated by exposure
of endothelium to tumor necrosis factor. Identification of endothelial cell %%%protein%%% %%%C%%% %%%receptor%%% as a member of the CD1/major
histocompatibility complex superfamily provides insights into the role of protein C in regulating the inflammatory response.

%%%1994%%%

15/3,AB/11 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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06422492 EMBASE No: 1996085709
The Glasup 2sup 6 residue of protein C is required for the %%%binding%%%
of protein C to thrombomodulin and endothelial cell %%%protein%%% %%%C%%%
%%%receptor%%%, but not to protein S and factor Va
Nishioka J.; Ido M.; Hayashi T.; Suzuki K.
Department of Molecular Pathobiology, Mie University School of Medicine,Tsu-city, Mie 514 Japan
Thrombosis and Haemostasis (THROMB. HAEMOST.) (Germany) 1996, 75/2
(275-282)
CODEN: THHAD ISSN: 0340-6245
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

A functionally defective protein C (PC)-Mie, detected in the plasma of a patient with hereditary thrombophilia, has Lys substituted for gamma-carboxyglutamic acid (Gla)sup 2sup 6 residue. The activation rate of PC-Mie by Protac or thrombin in the absence of Casup 2sup + and that by thrombin with native thrombomodulin (TM), recombinant soluble truncated TM
or on cultured endothelial cells in the presence of Casup 2sup + were all apparently lower than that of normal PC. The anticoagulant activity of Protac-activated PC (APC)-Mie on the plasma clotting time and the rate of inactivation of factor Va by APC-Mie in the presence of phospholipids were lower than those seen with normal APC, APC-Mie and normal APC %%%bound%%%
equally to protein S and to biotinyl-factor Va. However, neither PC-Mie nor APC-Mie %%%bound%%% to phospholipids and to cultured human endothelial
cells. It was similar to that observed with Gla-domainless PC/APC, but different from that seen with normal PC/APC. These results suggest that Glasup 2sup 6-dependent conformation is required for the %%%binding%%% of
PC/APC to phospholipids, TM and the surface of endothelial cell PC/APC receptor, but not to protein S and factor Va.

15/3,AB/12 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08488479 96124295
Cellular regulation of the protein C pathway.
Esmon CT; Fukudome K
Oklahoma Medical Research Foundation, Department of Pathology, University
of Oklahoma Health Sciences Center, Oklahoma City 73104, USA.
Seminars in cell biology (UNITED STATES) Oct %%%1995%%%, 6 (5)

p259-68
, ISSN 1043-4682 Journal Code: A60
Contract/Grant No.: R37 HL30340, HL, NHLBI; R01 HL 29807, HL, NHLBI .
Languages: ENGLISH
Document type: JOURNAL ARTICLE; REVIEW; REVIEW, TUTORIAL
The protein C anticoagulant pathway regulates thrombin formation. The pathway is triggered when thrombin %%%binds%%% to the endothelial cell
proteoglycan, thrombomodulin. Unlike thrombin, this complex is a potent activator of the protein C zymogen, but it cannot clot blood. Activated protein C %%%binds%%% to protein S on cell surfaces where it proteolytically inactivates coagulation factors Va and VIIIa. Activated protein C also %%%binds%%% to a newly identified endothelial %%%protein%%%
%%%C%%% %%%receptor%%% . Congenital deficiencies in this pathway are
associated with thrombotic disease, and inflammation can cause acquired deficiencies. Activated protein C appears to inhibit inflammation. Thus, this pathway modulates both coagulation and inflammation.

15/3,AB/13 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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08115399 95159086
High affinity %%%binding%%% sites for activated protein C and protein C
on cultured human umbilical vein endothelial cells. Independent of protein S and distinct from known ligands.
Bangalore N; Drohan WN; Orthner CL
Plasma Derivatives Laboratory, American Red Cross Holland Laboratory, Rockville, Maryland 20855.
Thrombosis and haemostasis (GERMANY) Sep %%%1994%%%, 72 (3) p465-74,
ISSN 0340-6245 Journal Code: VQ7
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Activated protein C (APC) is an antithrombotic serine proteinase having anticoagulant, profibrinolytic and anti-inflammatory activities. Despite its potential clinical utility, relatively little is known about its clearance mechanisms. In the present study we have characterized the interaction of APC and its active site blocked forms with human umbilical vein endothelial cells (HUVEC). At 4 degrees C 125I-APC %%%bound%%% to
HUVEC in a specific, time dependent, saturable and reversible manner. Scatchard analysis of the %%%binding%%% isotherm demonstrated a Kd value of
6.8 nM and total number of %%%binding%%% sites per cell of 359,000. Similar
%%%binding%%% isotherms were obtained using radiolabeled protein C (PC)
zymogen as well as D-phe-pro-arg-chloromethylketone (PPACK) inhibited APC
indicating that a functional active site was not required. Competition studies showed that the %%%binding%%% of APC, PPACK-APC and PC were
mutually exclusive suggesting that they %%%bound%%% to the same site(s).
Proteolytic removal of the N-terminal gamma-carboxyglutamic acid (gla) domain of PC abolished its ability to compete indicating that the gla-domain was essential for cell %%%binding%%%. Surprisingly, APC
%%%binding%%% to these cells appeared to be independent of protein S, a
cofactor of APC generally thought to be required for its high affinity %%%binding%%% to cell surfaces. The identity of the cell %%%binding%%%
site(s), for the most part, appeared to be distinct from other known APC ligands which are associated with cell membranes or extracellular matrix including phospholipid, thrombomodulin, factor V, plasminogen activator inhibitor type 1 (PAI-1) and heparin. Pretreatment of HUVEC with antifactor VIII %%%antibody%%% caused partial inhibition of 125I-APC %%%binding%%%
indicating that factor VIII or a homolog accounted for approximately 30% of APC %%%binding%%%. Studies of the properties of surface %%%bound%%%
125I-APC or 125I-PC and their fate at 4 degrees C compared to 37 degrees C
were consistent with association of approximately 25% of the initially %%%bound%%% radioligand with an endocytic receptor. However, most of the
radioligand appeared not to be %%%bound%%% to an endocytic receptor and
dissociated rapidly at 37 degrees C in an intact and functional state. These data indicate the presence of specific, high affinity %%%binding%%%
sites for APC and PC on the surface of HUVEC. While a minor proportion of
%%%binding%%% sites may be involved in endocytosis, the identity and
function of the major proportion is presently unknown. It is speculated that this putative receptor may be a further mechanisms of localizing the PC antithrombitic system to the vascular endothelium.

15/3,AB/14 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0194874 DBA Accession No.: 96-05645 PATENT
Isolated endothelial cell protein-C/activated %%%protein%%%-%%%C%%%
%%%receptor%%% - gene cloning and expression for use as an antiinflammatory or anticoagulant; inhibitory nucleic acid for use in cancer therapy; antitumor receptor-antagonist isolation
AUTHOR: Fukudome K; Esmon C T
CORPORATE SOURCE: Oklahoma City, OK, USA.
PATENT ASSIGNEE: Oklahoma-Med.Res.Found. %%%1996%%%
PATENT NUMBER: WO 9605303 PATENT DATE: 960222 WPI ACCESSION NO.:
96-139699 (9614)
PRIORITY APPLIC. NO.: US 289699 APPLIC. DATE: 940812
NATIONAL APPLIC. NO.: WO 95US9636 APPLIC. DATE: 950809
LANGUAGE: English
ABSTRACT: A new isolated human endothelial cell protein-C-activated-%%%protein%%%-%%%C%%% %%%receptor%%% has a specified DNA sequence or
derivative, and may be expressed on the surface of a non-human cell or non-endothelial cell, or may be in soluble form (lacking at least part of the transmembrane region). The DNA may be inserted in a vector for expression in a host cell. An inflammatory response may be enhanced by blocking %%%binding%%% of protein-C (EC-3.4.21.69) or activated
protein-C to the receptor using an %%%antibody%%% or fragment, inhibitory nucleic acid or other types of compound. An inflammatory response may be inhibited using the receptor or an agonist. These antiinflammatory compounds may be useful in therapy of e.g. Gram-negative bacterium sepsis, apoplexy, thrombosis, septic shock, acute respiratory distress syndrome or pulmonary embolism. Localization of the receptor to surfaces in contact with blood renders the surfaces anticoagulant by concentration of activated protein-C, so may be used in coating of vascular grafts. Receptor-antagonists may be useful as e.g. antitumor agents. (58pp)
? ds

Set	Items	Description
S1	27187	PROTEIN(W)C
S2	96	EPCR
S3	134	S1(W)RECEPTOR
S4	147	S2 OR S3
S5	1478948	ANTIBOD?
S6	7599752	TREAT? OR DIAGNOS?
S7	26	S4 AND S5
S8	3969	S1 AND S5
S9	1759385	BIND? OR BOUND
S10	2429	S1(N5)S9
S11	423	S10 AND S6
S12	76	S4 AND S9
S13	78	S7 OR S12
S14	39	RD (unique items)
S15	14	S14 AND PY<1998

? s s1(2n)s9

```
      27187  S1
    1759385  S9
   S16   1775  S1(2N)S9
? s s16 and s6

       1775  S16
    7599752  S6
   S17    329  S16 AND S6
? rd

...examined 50 records  (50)
...examined 50 records  (100)
...examined 50 records  (150)
...examined 50 records  (200)
...examined 50 records  (250)
...examined 50 records  (300)
...completed examining records
   S18    167  RD (unique items)
? s s18 and py<1998

Processing
        167  S18
   28044798  PY<1998
   S19     92  S18 AND PY<1998
? t s19/3,ab/1-92


 19/3,AB/1     (Item 1 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)
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11295524  BIOSIS NO.: 199800076856
CCAAT/enhancer-binding protein delta activates insulin-like growth factor-I
  gene transcription in osteoblasts: Identification of a novel cyclic AMP
  signalling pathway in bone.
AUTHOR: Umayahara Yutaka; Ji Changhua; Centrella Michael; Rotwein
Peter(a);
  McCarthy Thomas L
AUTHOR ADDRESS: (a)Oregon Health Sci. Univ., Dep. Med., Molecular
Med.
  Div., 3181 S.W. Sam Jackson Park Rd., Mail C**USA
JOURNAL: Journal of Biological Chemistry  272 (50):p31793-31800 Dec.
12,
%%%1997%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Insulin-like growth factor-I (IGF-I) plays a key role in skeletal
  growth by stimulating bone cell replication and differentiation. We
  previously showed that prostaglandin E2 (PGE2) and other cAMP-activating
  agents enhanced, IGF-I gene transcription in cultured primary rat
  osteoblasts through promoter 1, the major IGF-I promoter, and identified
  a short segment of the promoter, termed HS3D, that was essential for
  hormonal regulation of IGF-I gene expression. We now demonstrate that
  CCAAT/enhancer-%%%binding%%% %%%protein%%%
(%%%C%%%/EBP) delta is a major
  component of a PGE2-stimulated DNA-protein complex involving HS3D
and
  find that C/EBPdelta transactivates IGF-I promoter I through this site.
  Competition gel shift studies first indicated that a core C/EBP half-site
  (GCAAT) was required for binding of a labeled HS3D oligomer to
osteoblast
  nuclear proteins. Southwestern blotting and UV-cross-linking studies
  showed that the HS3D probe recognized a apprx 35-kDa nuclear protein,
and
  antibody supershift assays indicated that C/EBPdelta comprised most of
  the PGE2-activated gel-shifted complex. C/EBPdelta was detected by
  Western immunoblotting in osteoblast nuclear extracts after
  %%%treatment%%% of cells with PGE2. An HS3D oligonucleotide
competed
  effectively with a high affinity C/EBP site from the rat albumin gene for
  binding to osteoblast nuclear proteins. Cotransfection of osteoblast cell
  cultures with a C/EBPdelta expression plasmid enhanced basal and
  PGE2-activated IGF-I promoter 1-luciferase activity but did not stimulate
  a reporter gene lacking an HS3D site. By contrast, an expression plasmid
  for the related protein, C/EBPbeta, did not alter basal IGF-I gene
  activity but did increase the response to PGE2. In osteoblasts and in
  COS-7 cells, C/EBPdelta, but not C/EBPbeta, transactivated a reporter
  gene containing four tandem copies of HS3D fused to a minimal promoter;
  neither transcription factor stimulated a gene with four copies of an
  HS3D mutant that was unable to bind osteoblast nuclear proteins. These
  results identify C/EBPdelta as a hormonally activated inducer of IGF-I
  gene transcription in osteoblasts and show that the HS3D element within
  IGF-I promoter 1 is a high affinity binding site for this protein.

%%%1997%%%


 19/3,AB/2     (Item 2 from file: 5)
DIALOG(R)File  5:Biosis Previews(R)
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11264512  BIOSIS NO.: 199800045844
Transcription factor C/EBPdelta in fetal lung: Developmental regulation and
  effects of cyclic adenosine 3',5'-monophosphate and glucocorticoids.
AUTHOR: Breed David R; Margraf Linda R; Alcorn Joseph L; Mendelson
Carole R
  (a)
AUTHOR ADDRESS: (a)Dep. Biochem., Univ. Texas Southwestern Med.
Center,
  5323 Harry Hines Blvd., Dallas, TX 75235-90**USA
JOURNAL: Endocrinology  138 (12):p5527-5534 Dec., %%%1997%%%
ISSN: 0013-7227
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Pulmonary surfactant is a developmentally and hormonally
  regulated lipoprotein synthesized exclusively in alveolar type II cells.
  Surfactant protein-A (SP-A) gene transcription in human fetal lung in
  culture is stimulated by glucocorticoids and cAMP; cAMP also enhances the
  rate of type II cell differentiation. The
CCAAT/enhancer-%%%binding%%%
  %%%protein%%% (%%%C%%%/EBP) family of transcription factors
serves an
  important role in the regulation of genes involved in energy metabolism,
  lipid biosynthesis, and cellular differentiation. The gene encoding
  C/EBPdelta, which is induced by glucocorticoids during the early phases
  of adipocyte differentiation, is expressed at relatively high levels in
  lung compared with other tissues. In the present study we have analyzed
  developmental changes in C/EBPdelta messenger RNA levels in fetal rabbit
  lung as well as changes in the levels of immunoreactive C/EBPdelta in
  human fetal lung during differentiation in organ culture and after
  %%%treatment%%% with cAMP and glucocorticoids. We observed that
  C/EBPdelta messenger RNA is detectable in fetal rabbit lung on day 19 of
  gestation and is increased -3.7-fold to maximum levels on day 28 of
  gestation, the time when SP-A gene transcription increases to maximum
  levels. Immunohistochemical analysis of C/EBPdelta in midgestation human
  fetal lung before culture revealed trace nuclear staining in epithelial
  and occasional stromal cells. After 12 h of organ culture in serum-free
  medium, nuclear staining of C/EBPdelta was markedly increased in
  epithelial cells lining the prealveolar ducts of the human fetal lung
  tissue. By immunoblot analysis, it was found that C/EBPdelta levels were
  induced rapidly during organ culture in control medium and were increased
  further by %%%treatment%%% with dexamethasone and (Bt)2cAMP.
C/EBPdelta
  levels were maximally induced during the first 24 h of culture and
  declined thereafter; after 72 h of incubation in control or
  cAMP-containing medium, C/EBPdelta was reduced markedly. By contrast,
in
  fetal lung tissues incubated in medium containing dexamethasone or
  dexamethasone plus (Bt)2cAMP, the decline in C/EBPdelta was more
modest,
  so that levels remained elevated throughout the 96-h culture period. Our
  findings that C/EBPdelta is localized primarily to alveolar epithelial
  cells, rapidly induced during differentiation of human fetal lung in
  culture, and increased by cAMP and glucocorticoids suggest a possible
  role in the regulation of type II cell differentiation and in the
  synthesis of surfactant phospholipids and proteins.

%%%1997%%%


 19/3,AB/3     (Item 3 from file: 5)
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DIALOG(R)File 5:Biosis Previews(R)
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11261929 BIOSIS NO.: 199800043261
Physical activity and biochemical markers of bone turnover in elderly patients.
AUTHOR: Ricciotti Roberto(a); Gemini Rossano; Foschi Ferdinando; Dubbini Stefania; Fattoretti Patrizia; Bertoni-Freddari Carlo
AUTHOR ADDRESS: (a)Radiochemistry Lab., INRCA, Via della Montagonal 164, 60131 Ancona**Italy
JOURNAL: Archives of Gerontology and Geriatrics 26 (1):p49-53 Dec., %%%1997%%%
ISSN: 0167-4943
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To assess the role of physical therapy in improving the remodelling processes of bone turnover, biochemical markers of bone formation and resorption (osteocalcin, parathormone, bone-specific alkaline phosphatase, somatotropic hormone, C-terminal propeptide type I procollagen, somatomedin, insulin-like growth factor %%%bound%%% %%%protein%%%, %%%C%%%-terminal telopeptide type I collagen) have been investigated in elderly patients before and after a cycle of physical therapy. Patients of both sexes, immobilized on hospital admission day because of fractures or neurologic diseases, underwent physiotherapy for one month. Following physical %%%treatment%%% we found significant increases of osteocalcin, bone-specific alcaline phosphatase and somatomedin in the female group, while no significant difference was detected in males. Our data support that the mechanical stimulus significantly improves the recovery of osteoblastic activity in women, while in men the increases in bone remodelling markers are not significant. Differences in life-style between male and female patients are proposed as determinants in the bone remodelling response to physical therapy.

%%%1997%%%

19/3,AB/4 (Item 4 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11248145 BIOSIS NO.: 199800029477
Clinical characteristics of familial hypertrophic cardiomyopathy caused by the Phe110Ile mutation in the cardiac troponin T gene: Analysis of 6 families.
AUTHOR: Shono Hirohisa(a)
AUTHOR ADDRESS: (a)First Dep. Internal Med., Fac. Med., Kagoshima Univ., Kagoshima 890**Japan
JOURNAL: Medical Journal of Kagoshima University 49 (2):p117-128 Aug., %%%1997%%%
ISSN: 0368-5063
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: Japanese; Non-English
SUMMARY LANGUAGE: Japanese; English

ABSTRACT: To clarify the genetic and clinical features of familial hypertrophic cardiomyopathy (FHC) caused by a Phe110Ile mutation in the cardiac troponin T (TnT) gene, 6 families with Phe110Ile mutation were studied. Forty-six probands (24 males, 22 females, age 57.4+-17.1 years old) with FHC were screened for mutations in beta cardiac myosin heavy chain, alpha-tropomyosin, TnT and cardiac myosin %%%binding%%% %%%protein%%%-%%%C%%% genes. Phe110Ile mutation in TnT gene was found in probands. Family survey was done in the 6 families. Genetic analyses were done with mutation analysis and haplotype analysis. Clinical analyses were done with electrocardiograms and echocardiograms. Left ventricular hypertrophy was evaluated with echocardiograms. According to Maron's criteria, distribution of the hypertrophy was classified into type I, II, III and IV. Apical hypertrophy was classified as type IV (A). Genotyping of angiotensin-I converting enzyme (ACE) gene was done in 14 members in 4 families. Phenotype of the 6 probands was type II in 2 probands, type III in 2 (1 with left ventricular outflow obstruction) and type IV(A) in 2. Twenty members in 6 families were analyzed genetically and clinically. Sixteen (5 males, 11 females, age 47.9+-16.6 years old) were affected with Phe110Ile mutation by mutation analysis. Two of the 6 families will be the same origin by haplotype analysis, while 4 will be different each other. Phenotype of the affected members was type II in 4 members, type III in 6 (1 with left ventricular outflow obstruction), type IV (A) in 3 and nonpenetrance in 3. Mean maximal wall thickness of the left ventricle in affected subjects was 17.3+-4.8mm, and penetrance of the mutation was 81%. More than 2 affected members were analyzed in 4 families. Phenotype of 2 affected members was same in 1 family, but phenotype of affected members were different in other 3 families. In one family, phenotype was type IV(A) in 2 members, nonpenetrnce was in 1. In another family, phenotype was type IV (A) in 1 member, type II in 1, type III in 2, nonpenetrance in 1. In the other family, phenotype was type II in 2 members, type III in 1, nonpenetrance in 1. No correlation was found with ACE genotype and wall thickness nor type of the hypertrophy. It was suggested that distribution of the hypertrophy was various (type II, III, IV(A)) in FHC with Phe110Ile mutation in TnT gene, and that it was not always identical within a family.

%%%1997%%%

19/3,AB/5 (Item 5 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11177515 BIOSIS NO.: 199799798660
Hepatic expression of CCAAT/enhancer binding protein alpha: Hormonal and metabolic regulation in rats.
AUTHOR: Crosson S M; Davies G F; Roesler W J(a)
AUTHOR ADDRESS: (a)Dep. Biochem., Univ. Sask., 107 Wiggins Rd., Saskatoon, SK S7N 5E5**Canada
JOURNAL: Diabetologia 40 (10):p1117-1124 %%%1997%%%
ISSN: 0012-186X
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: There is a significant body of evidence which suggests that the alpha-isoform of the CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%% /EBP-alpha) plays a central regulatory role in energy metabolism in the liver. However, there is little information available regarding regulation of its expression in this tissue. In this study, we examined the effect of hormones and diabetes on its expression in rat H4IIE hepatoma cells and in rat liver. %%%Treatment%%% of H4IIE cells with dexamethasone led to a threefold increase in C/EBP-alpha mRNA within 4 h. Insulin %%%treatment%%% produced a bi-phasic response, initially reducing mRNA levels up to the 4 h time point, but after 8 h a twofold increase in C/EBP-alpha mRNA was observed. %%%Treatment%%% with 8-chlorophenylthio-cAMP produced a twofold induction of C/ EBP-alpha mRNA after 8 h. Western analysis indicated that the changes in mRNA in response to hormonal %%%treatment%%% generally resulted in corresponding alterations in C/EBP-alpha protein levels. Finally, we observed an inhibition of C/EBP-alpha gene expression in streptozotocin-diabetic rat liver, reflected by a decrease in both mRNA and protein levels that were partially reversed by insulin %%%treatment%%%. These results indicate that the expression of C/EBP-alpha in liver is under complex control by both hormonal and metabolic signals, which is consistent with its role as a trans-regulator of genes which play a role in energy metabolism.

%%%1997%%%

19/3,AB/6 (Item 6 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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11023149 BIOSIS NO.: 199799644294
Thrombomodulin gene mutations associated with myocardial infarction.

AUTHOR: Ireland Helen(a); Kunz Gabriella; Kyriakoulis Konstantinos; Stubbs
Peter J; Lane David A
AUTHOR ADDRESS: (a)Haematol. Dep., Charing Cross Westminster Med. Sch., St.
Dunstans Rd., London W6 8RP**UK
JOURNAL: Circulation 96 (1):p15-18 %%%1997%%%
ISSN: 0009-7322
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Background: Thrombomodulin is an important receptor for thrombin
on the endothelial cell surface of most blood vessels, including those of the heart. Thrombin-%%%bound%%% thrombomodulin activates %%%protein%%%
%%%C%%%, which inhibits thrombin generation by degrading factors Va and
VIIIa. The aim of this study was to analyze the 5' region of the thrombomodulin gene to determine whether mutations contribute a risk for myocardial infarction. Methods and Results: We screened the promoter region of the thrombomodulin gene by single-stranded conformation polymorphism analysis in 104 patients with %%%diagnosed%%% myocardial
infarction. Five mutations (three distinct) were identified (GG-9/-10AT, G-33A, and C-133A). The dinucleotide mutation GG-9/-10AT was identified
in 3 individuals (2 heterozygous, 1 homozygous). Only one of the three different mutations was identified in 104 patient control subjects matched for age, sex, and race (G-33A in a single individual). All mutations identified were in close proximity to consensus sequences for transcription control elements within the thrombomodulin gene. In contrast, no difference was observed between patients and control subjects for the allelic frequency of a previously identified neutral polymorphism GCC/GTC coding for Ala/Val-455, with 3 individuals homozygous for GTC (Val) in both groups. Conclusions The findings suggest
that mutations in the promoter region of the thrombomodulin gene may constitute a risk for arterial thrombosis.

%%%1997%%%

19/3,AB/7 (Item 7 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10989822 BIOSIS NO.: 199799610967
CCAAT/enhancer binding protein epsilon is preferentially up-regulated during granulocytic differentiation and its functional versatility is determined by alternative use of promoters and differential splicing.
AUTHOR: Yamanaka Ryuya; Kim Gun-Do; Radomska Hanna S; Lekstrom-Himes Julie;
Smith Laura T; Antonson Per; Tenen Daniel G; Xanthopoulos Kleanthis G(a)
AUTHOR ADDRESS: (a)Clinical Gene Therapy Branch, Natl. Hum. Genome Res.
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JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 94 (12):p6462-6467 %%%1997%%%
ISSN: 0027-8424
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) epsilon
is a recently cloned member of the C/EBP family of transcription factors and is expressed exclusively in cells of hematopoietic origin. The human C/EBP-epsilon gene is transcribed by two alternative promoters, P-alpha and P-beta. A combination of differential splicing and alternative use of promoters generates four mRNA isoforms, of 2.6 kb and 1.3-1.5 kb in size. These transcripts can encode three proteins of calculated molecular mass 32.2 kDa, 27.8 kDa, and 14.3 kDa. Accordingly, Western blots with antibodies specific for the DNA-binding domain, that is common to all forms, identify multiple proteins. C/EBP-epsilon mRNA was greatly induced during in vitro granulocytic differentiation of human primary CD34+ cells. Retinoic acid %%%treatment%%% of HL60 promyelocytic leukemia cells
for 24 hr induced C/EBP-epsilon mRNA levels by 4-fold, while prolonged %%%treatment%%% gradually reduced mRNA expression to pretreatment levels.
Transient transfection experiments with expression vectors for two of the isoforms demonstrated that the 32.2-kDa protein is an activator of transcription of granulocyte colony-stimulating factor receptor promoter, while the 14.3-kDa protein is not. Thus, C/EBP-epsilon is regulated in a complex fashion and may play a role in the regulation of genes involved in myeloid differentiation.

%%%1997%%%

19/3,AB/8 (Item 8 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10970292 BIOSIS NO.: 199799591437
Cardiomyopathies.
AUTHOR: Schwartz Ketty
AUTHOR ADDRESS: IFR n. 14, INSERM UR 153, Inst. Myol., Groupe Hosp.
Pitie-Salpetriere, 47 boulevard de l'Hopital, 75**France
JOURNAL: Pathologie Biologie 45 (3):p213-217 %%%1997%%%
ISSN: 0369-8114
RECORD TYPE: Abstract
LANGUAGE: English
SUMMARY LANGUAGE: English; French

ABSTRACT: Cardiomyopathies, and more specifically hypertrophic cardiomyopathy, have opened the route to what is now called genetic cardiology. Hypertrophic cardiomyopathy (HCM) is characterized by unexplained left and/or right ventricular hypertrophy, and disorganization of tissular architecture. Approximately 60% of HCM are transmitted as an autosomal dominant trait. The clinical aspects of HCM vary markedly, and several morphological variants were described, depending on the localization of hypertrophy. This pathology is often complicated by cardiac failure, but the major risk is sudden death, and the predictive factors are presently very unrefined. Several pathogenic hypotheses were forwarded in the past, and one surprising result of genetic analyses is that none of these hypotheses was confirmed. Four disease genes were identified, and they encode sarcomeric proteins, cardiac myosin heavy chain, troponin T, tropomyosin and cardiac myosin %%%binding%%% %%%protein%%% %%%C%%%. To this high intergenic
heterogeneity is associated a high intragenic heterogeneity. A major fall out of these genetic findings is the recent discovery of adult healthy carriers, around 30% in our experience. Genotype/phenotype relationships are being performed, and this is the first approach to a prognostic evaluation based on genetic localization. The work on hypertrophic cardiomyopathy is currently being used as a model to analyse dilated cardiomyopathies, characterized by dilatation and impaired contraction of the left or both ventricles. The mode of inheritance of these forms of cardiomyopathies is complex. Five families with an autosomal inheritance were analyzed since two years, the loci were found, but the disease genes are not identified yet. Identification of patients at high risk and early %%%treatment%%% or prevention are the current goals.

%%%1997%%%

19/3,AB/9 (Item 9 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10834266 BIOSIS NO.: 199799455411
Functional antagonism between CCAAT/enhancer binding protein-alpha and peroxisome proliferator-activated receptor-gamma on the leptin promoter.
AUTHOR: Hollenberg Anthony N; Susulic Vedrana S; Madura John P; Zhang Bei;
Moller David E; Tontonoz Peter; Sarraf Pasha; Spiegelman Bruce M; Lowell
Bradford B(a)
AUTHOR ADDRESS: (a)Division Endocrinol., Beth Israel Hosp., Harvard Med.
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JOURNAL: Journal of Biological Chemistry 272 (8):p5283-5290 %%%1997%%%

ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The ob gene product, leptin, is a major hormonal regulator of appetite and fat cell mass. Recent work has suggested that the antidiabetic agents, the thiazolidinediones (TZ), which are also high affinity ligands of peroxisome proliferator-activated receptor-gamma (PPAR-gamma), inhibit leptin expression in rodents. To examine the effects of this class of drug on the leptin gene in adipocytes we performed Northern analysis on primary rat adipocytes cultured in the presence or absence of TZ. TZ reduced leptin mRNA levels by 75%. To determine whether this effect was mediated at the transcriptional level, we isolated 6510 base pairs of 5'-flanking sequence of the leptin promoter and studied reporter constructs in primary rat adipocytes and CV-1 cells. Sequence analysis demonstrated the presence of a consensus direct repeat with a 1-base-pair gap site between -3951 and -3939 as well as a consensus CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) site between -55 and -47. Our functional analysis in transfected primary rat adipocytes demonstrates that, despite the presence of a canonical direct repeat with a 1-base-pair gap site, TZ alone decreases reporter gene expression of leptin promoter constructs ranging from -6510 to +9 to -65 to +9. In CV-1 cells, which contain endogenous PPAR-gamma, TZ %%%treatment%%% alone had little effect on these constructs. However, TZ %%%treatment%%% did inhibit C/EBPa-mediated transactivation of the leptin promoter. This down-regulation of leptin reporter constructs mapped to a -65 to +9 promoter fragment which binds C/EBP-alpha in gel-mobility shift assays but does not bind PPAR-gamma-2 alone or as a heterodimer with 9-cis-retinoic acid receptor. Conversely, the promoter (-5400 to +24 base pairs) of the aP2 gene, another adipocyte-specific gene, was induced 7.3-fold by TZ. Co-transfection with C/EBP-alpha minimally stimulated the aP2 promoter from basal levels but notably blocked activation by TZ. These data indicate that PPAR-gamma and C/EBP-alpha can functionally antagonize each other on at least two separate promoters and that this mechanism may explain the down-regulation of leptin expression by thiazolidinediones.

%%%1997%%%

19/3,AB/10 (Item 10 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10802420 BIOSIS NO.: 199799423565
The glucocorticoid-responsive gene cascade: Activation of the rat arginase gene through induction of C/EBP-beta.
AUTHOR: Gotoh Tomomi; Chowdhury Shoaib; Takiguchi Masaki(a); Mori Masataka
AUTHOR ADDRESS: (a)Dep. Molecular Genetics, Kumamoto Univ. Sch. Med., Kuhonji 4-24-1, Kumamoto 862**Japan
JOURNAL: Journal of Biological Chemistry 272 (6):p3694-3698 %%%1997%%%
ISSN: 0021-9258
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The gene for liver-type arginase, an ornithine cycle enzyme, is induced by glucocorticoids in a delayed secondary manner. An enhancer element located around intron 7 of the rat arginase gene shows delayed glucocorticoid responsiveness, and it harbors two sites binding with members of the CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) family. Here, we investigate the role of these C/EBP binding sites in glucocorticoid response of the arginase gene. When inserted in front of the herpes simplex virus thymidine kinase promoter, these C/EBP sites exhibited glucocorticoid responsiveness in reporter transfection assay using rat hepatoma H4IIE cells. In footprint analysis using nuclear extracts of H4IIE cells, profiles of the protected areas of the two C/EBP sites changed when cells were %%%treated%%% with dexamethasone. In gel shift analysis, the complex formation for the two C/EBP sites was augmented in response to dexamethasone. Antibody supershift/inhibition analysis demonstrated that a major portion of the binding proteins induced by dexamethasone is C/EBP-beta. Induction of arginase mRNA by dexamethasone was preceded by augmentation of the C/EBP site-binding activities, which followed increase in C/EBP-beta mRNA. These results were consistent with the notion that the glucocorticoid response of the arginase gene is mediated by C/EBP-beta.

%%%1997%%%

19/3,AB/11 (Item 11 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10613362 BIOSIS NO.: 199699234507
Regulation of CCATT/enhancer-binding protein family members by stimulation of glutamate receptors in cultured rat cortical astrocytes.
AUTHOR: Yano Shigetoshi; Fukunaga Kohji(a); Takiguchi Masaki; Ushio Yukitaka; Mori Masataka; Miyamoto Eishichi
AUTHOR ADDRESS: (a)Dep. Pharmacol., Kumamoto Univ. Sch. Med., 2-2-1, Honjo, Kumamoto 860**Japan
JOURNAL: Journal of Biological Chemistry 271 (38):p23520-23527 %%%1996%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Regulation of mRNA levels, DNA binding activities, and phosphorylation of CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%% /EBP) family members by stimulation of glutamate receptors were studied in cultured rat cortical astrocytes. Indirect immunofluorescence and immunoblot analyses with specific antibodies to C/EBP family members revealed that both C/EBP-beta and C/EBP-delta but not C/EBP-alpha are expressed in the nuclei of astrocytes. After exposure to glutamate, C/EBP-beta mRNA levels increased within 10 min, reached the maximal level at about 1 h, and returned to the basal level within 6 h. In contrast, C/EBP-delta mRNA levels decreased by 6 h and were recovered within 12 h. These changes in mRNA levels were accompanied by an increase and a decrease in proteins for C/EBP-beta and C/EBP-delta, respectively. Elevation of C/EBP-beta mRNA levels by glutamate %%%treatment%%% required an increase in intracellular Ca-2+ concentration and depended on activations of protein kinase C and calmodulin-dependent protein kinases. Gel mobility shift analysis using nuclear extracts from the glutamate-%%%treated%%% cells showed increases in C/EBP site binding activities 2 h after the exposure to glutamate. Moreover, glutamate stimulated phosphorylation of C/EBP-beta in 32P-labeled astrocytes in a Ca-2+-dependent manner. These results suggest that glutamate regulates functions of C/EBP family members in brain astrocytes through changes in mRNA levels of C/EBP-beta and C/EBP-delta as well as through phosphorylation of C/EBP-beta.

%%%1996%%%

19/3,AB/12 (Item 12 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10578217 BIOSIS NO.: 199699199362
CAMP activation of phosphoenolpyruvate carboxykinase transcription in renal LLC-PK-1-F+ cells.
AUTHOR: Liu Xiangdong; Curthoys Norman P(a)
AUTHOR ADDRESS: (a)Dep. Biochemistry Molecular Biol., Colorado State Univ., Fort Collins, CO 80523-1870**USA
JOURNAL: American Journal of Physiology 271 (2 PART 2):pF347-F355 %%%1996%%%
ISSN: 0002-9513
DOCUMENT TYPE: Article
RECORD TYPE: Abstract

LANGUAGE: English

ABSTRACT: Phosphoenolpyruvate carboxykinase (PCK) is a key regulatory enzyme in renal ammoniagenesis and gluconeogenesis. LLC-PK-1-F+ cells are porcine renal proximal tubule-like cells that express significant levels of the cytosolic PCK. %%%Treatment%%% of subconfluent LLC-PK-1-F+ cells with 0.1 mM 8-(4-chlorophenylthio)adenosine 3',5'-cyclic monophosphate (CPT-cAMP) for 8 h causes a 21-fold increase in PCK mRNA. This response is very rapid and is not inhibited by 0.5 mM cycloheximide, indicating that ongoing protein synthesis is not required. Similarly, cells transfected with PCK-490CAT exhibit an 8- to 10-fold increase in chloramphenicol acetyltransferase (CAT) activity when %%%treated%%% with cAMP for 24 h. The addition of okadaic acid, a protein phosphatase inhibitor, both stimulated the CAT activity and potentiated the cAMP effect by twofold, suggesting that phosphorylation may contribute to the transcriptional activation. Assays using a series of PCK-CAT constructs containing specific deletions or block mutations established that the CRE-1 the P3(II) elements are required for the cAMP response. Cotransfection experiments using dominant negative expression vectors indicated that a CCAAT enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) transcription factor, and not CREB, mediates cAMP activation of transcription in LLC-PK-1-F+ cells.

%%%1996%%%

19/3,AB/13 (Item 13 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10526383 BIOSIS NO.: 199699147528
Alteration of myosin cross bridges by phosphorylation of myosin-%%%binding%%% %%%protein%%% %%%C%%% in cardiac muscle.
AUTHOR: Weisberg Andrea; Winegrad Saul(a)
AUTHOR ADDRESS: (a)Dep. Physiol., Sch. Med., Univ. Pennsylvania, Philadelphia, PA 19104-6085**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 93 (17):p8999-9003 %%%1996%%%
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: In addition to the contractile proteins actin and myosin, contractile filaments of striated muscle contain other proteins that are important for regulating the structure and the interaction of the two force-generating proteins. In the thin filaments, troponin and tropomyosin form a Ca-sensitive trigger that activates normal contraction when intracellular Ca is elevated. In the thick filament, there are several myosin-binding proteins whose functions are unclear. Among these is the myosin-%%%binding%%% %%%protein%%% %%%C%%% (MBP-C). The cardiac isoform contains four phosphorylation sites under the control of cAMP and calmodulin-regulated kinases, whereas the skeletal isoform contains only one such site, suggesting that phosphorylation in cardiac muscle has a specific regulatory function. We isolated natural thick filaments from cardiac muscle and, using electron microscopy and optical diffraction, determined the effect of phosphorylation of MBP-C on cross bridges. The thickness of the filaments that had been %%%treated%%% with protein kinase A was increased where cross bridges were present. No change occurred in the central bare zone that is devoid of cross bridges. The intensity of the reflections along the 43-nm layer line, which is primarily due to the helical array of cross bridges, was increased, and the distance of the first peak reflection from the meridian along the 43-nm layer line was decreased. The results indicate that phosphorylation of MBP-C (i) extends the cross bridges from the backbone of the filament and (ii) increases their degree of order and/or alters their orientation. These changes could alter rate constants for attachment to and detachment from the thin filament and thereby modify force production in activated cardiac muscle.

%%%1996%%%

19/3,AB/14 (Item 14 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10510793 BIOSIS NO.: 199699131938
Tumor necrosis factor alpha promotes nuclear localization of cytokine-inducible CCAAT/enhancer binding protein isoforms in hepatocytes.
AUTHOR: Yin Ming; Yang Shi Qui; Lin Hui Zhi; Lane M Daniel; Chatterjee Subroto; Diehl Anna Mae(a)
AUTHOR ADDRESS: (a)912 Ross Bldg., Johns Hopkins Univ., 720 Rutland St., Baltimore, MD 21205**USA
JOURNAL: Journal of Biological Chemistry 271 (30):p17974-17978 %%%1996%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Hepatocytes were cultured in the presence of recombinant tumor necrosis factor (TNF) alpha or mutated TNF alpha peptides that specifically activate either p55 or p75 TNF receptors to determine if TNF alpha can activate cytokine-inducible CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) isoforms by post-transcriptional mechanisms that are initiated by TNF receptors. Within 5-10 min after %%%treatment%%% with any of these agents, nuclear concentrations of C/EBP beta and C/EBP delta double and remain 2-4-fold greater than control cultures for 30 min (p lt 0.01). Consistent with these results, gel mobility shift assays demonstrate 3-fold increased nuclear C/EBP beta- and C/EBP delta-DNA binding activity in TNF alpha-%%%treated%%% cells, and immunocytochemistry confirms rapid redistribution of these C/EBP isoforms into the nucleus. In contrast, mRNA and whole cell protein concentrations of C/EBP beta and delta are not altered by TNF alpha exposure, and nuclear concentrations of another C/EBP isoform, C/EBP alpha, are decreased by 80%. This novel evidence that TNF alpha initiates post-transcriptional activation of cytokine-inducible C/EBP isoforms identifies a mechanism that enables hepatocytes to respond immediately to inflammatory stress.

%%%1996%%%

19/3,AB/15 (Item 15 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10469728 BIOSIS NO.: 199699090873
GADD153/CHOP, a DNA damage-inducible protein, reduced CAAT/enhancer binding protein activities and increased apoptosis in 32D c13 myeloid cells.
AUTHOR: Friedman Alan D
AUTHOR ADDRESS: Johns Hopkins Oncol. Center, Room 3-109, 600 North Wolfe St., Baltimore, MD 21287**USA
JOURNAL: Cancer Research 56 (14):p3250-3256 %%%1996%%%
ISSN: 0008-5472
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: GADD153/CHOP is a DNA damage-inducible, nuclear leucine zipper protein that is capable of producing a G-1-S arrest in fibroblastic cells and of dimerizing with and inhibiting CAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) activities. CHOP was induced in 32D cl3 myeloid cells exposed to methylmethane sulfonate (MMS), a DNA alkylating agent. The degree of induction was dependent upon the dose of MMS to which the cells were exposed. CHOP was not expressed, at least at similar levels, during 32D cl3 cell granulocytic differentiation or during their apoptosis upon growth factor withdrawal. High-level expression of exogenous CHOP in 32D cl3 cells markedly inhibited the trans-activation

activities of endogenous C/EBPs. These cells proliferated in IL-3, although low-level ongoing apoptosis not observed with control cells was detected. When these cultures were transferred to granulocyte colony-stimulating factor (G-CSF), the majority of the cells underwent apoptosis, although the levels of CHOP did not increase. Similarly, 32D cl3 cells %%%treated%%% with doses of MMS sufficient to induce endogenous
CHOP underwent apoptosis more rapidly when placed in G-CSF-containing, compared with interleukin 3 (IL-3)containing, medium. However, induction of CHOP by MMS was similar in IL-3 and in G-CSF. The heightened sensitivity of 32D cl3 cells to CHOP in G-CSF could result either from the loss of IL-3-specific signals or from increased expression of C/EBPs. Because myeloid leukemias express C/EBPa, induction of CHOP might contribute to their chemotherapy-induced apoptosis, and alterations in CHOP expression could contribute to their development of chemotherapy resistance.

%%%1996%%%

19/3,AB/16 (Item 16 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10465222 BIOSIS NO.: 199699086367
C/EBP-beta is a negative regulator of human papillomavirus type 11 in keratinocytes.
AUTHOR: Wang Hao; Liu Kai; Yuan Fang; Berdichevsky Lillian; Taichman Lorne
B; Auborn Karen(a)
AUTHOR ADDRESS: (a)Dep. Otolaryngology, 270-05 76th Ave., Long Island
Jewish Med. Cent., New Hyde Park, NY 11040**USA
JOURNAL: Journal of Virology 70 (7):p4839-4844 %%%1996%%%
ISSN: 0022-538X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: We have evaluated the impact of the CCAAT enhancer-%%%binding%%%
%%%protein%%% (%%%C%%%/EBP) transcription factors on human papillomavirus
type 11 (HPV11). C/EBP-beta is in nuclei of cultured foreskin keratinocytes and binds its consensus sequence in HPV11 DNA. We have used
the novel approach of depleting the availability of C/EBPs in vivo using nuclease-resistant oligomers containing C/EBP DNA binding sites. In cultured foreskin keratinocytes containing replicating HPV11 DNA, levels of both HPV11 transcripts and HPV DNA increase after %%%treatment%%% with
oligomers containing the C/EBP-beta DNA binding motif. These results indicate that C/EBP-beta is a repressor for HPV11 in keratinocytes.

%%%1996%%%

19/3,AB/17 (Item 17 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10433764 BIOSIS NO.: 199699054909
Involvement of CCAAT/enhancer-binding protein and nuclear factor-kappa-B binding sites in interleukin-6 promoter inhibition by estrogens.
AUTHOR: Galien Rene; Evans Helen F; Garcia Teresa(a)
AUTHOR ADDRESS: (a)Roussel Uclaf, 102 Route Noisy, Romainvilee Cedex 93235
**France
JOURNAL: Molecular Endocrinology 10 (6):p713-722 %%%1996%%%
ISSN: 0888-8809
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Bone loss observed in postmenopausal women is clearly associated
with a decrease in estrogen levels. Interleukin 6 (IL-6), a multifunctional cytokine involved in osteoclast differentiation, is secreted by osteoblasts and appears to be a key molecule in the osteoporotic process. As previous reports have shown that the human IL-6 promoter is inhibited by estradiol, we investigated the mechanism of estradiol (E-2)-mediated IL-6 inhibition in human cells. Analysis of the IL-6 secretion as a function of time in osteoblastoma Saos-2 cells, using an IL-6 ELISA test, showed that a maximal E-2 inhibition of tumor necrosis factor-alpha (TNF-alpha) induction could be monitored between 2 and 24 h of %%%treatment%%%. IL-6 inhibition was clearly estrogen agonist-specific in Saos-2 and MCF7 cells. Transient transfections of HeLa cells with a pIL-6/CAT plasmid and an estrogen receptor (human ER) expression vector, confirmed the role of the human ER in inhibition of the IL-6 promoter. Deletion and mutational analysis of the promoter highlighted the role of the -185/-60 region and showed that in both MCF7 and HeLa cells, the nuclear factor-IL 6 (NF-IL6) site cooperates with the nuclear factor-kappa-B (NF-kappa-B) motif to produce maximal induction by
TNF-alpha, whereas the CCAAT/enhancer-%%%binding%%% %%%protein%%% (
%%%C%%%/EBP) site displayed different cooperative effects toward NF-kappa-B depending on the cell line used. In HeLa cells, but not in MCF7 cells, we defined an essential role for the C/EBP site by showing that the E-2 sensitivity was clearly dependent on its integrity. In these cell lines, the NF-kappa-B site mutation abrogated both the TNF-alpha- and E-2- sensitivity of the construct.

%%%1996%%%

19/3,AB/18 (Item 18 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

10433561 BIOSIS NO.: 199699054706
Alteration by 2,3,7,8-tetrachlorodibenzo-p-dioxin of CCAAT/enhancer binding
protein correlates with suppression of adipocyte differentiation in 3T3-L1 cells.
AUTHOR: Liu Phillip C C; Phillips Marjorie A; Matsumura Fumio(a)
AUTHOR ADDRESS: (a)Dep. Environ. Toxicol., Cent. Environ. Health Sci., Univ. Calif., Davis, CA 95616**USA
JOURNAL: Molecular Pharmacology 49 (6):p989-997 %%%1996%%%
ISSN: 0026-895X
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: 2,3,7,8-Tetrachlorodibenzo-p-dioxin (TCDD) and related compounds
elicit multiple effects on the function of adipose tissue and adipogenic cell lines, including the suppression of adipocyte differentiation. We began to examine the mechanism by which TCDD inhibits differentiation of the established preadipocyte cell line 3T3-L1. Examination of the expression of several early marker genes of preadipocyte differentiation through Northern blot analysis and of differentiation-dependent mitosis showed that TCDD did not interfere with the earliest known responses of preadipocytes to inducers of differentiation. Analysis of mRNA for three isoforms of the CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP)
revealed that TCDD (5 nM) selectively inhibited the induction of C/EBP-alpha mRNA but did not block the induction of C/EBP-beta and C/EBP-delta in response to differentiation inducers. The differentiation-dependent induction of PPAR-gamma mRNA was also blocked
by TCDD. Immunoblot analysis with specific antibodies to each C/EBP isoform demonstrated that the levels of C/EBP-delta and C/EBP-beta protein were rapidly induced (by day 1) and then abrogated by day 4 and 8, respectively, in solvent-%%%treated%%% (control) cells. In TCDD-%%%treated%%% cells, however, the levels of C/EBP-beta and C/EBP-delta
protein persisted at these time points. In contrast, C/EBP-alpha protein was markedly suppressed by TCDD in concordance with its level of RNA. Both translational products of C/EBP-alpha, p30 and p42, were dose-dependently decreased by TCDD. Gel shift analysis of nuclear extract binding to an oligonucleotide containing a C/EBP DNA recognition sequence
revealed no difference between extracts from control and TCDD-%%%treated%%% cells in the binding pattern at day 2 of differentiation. At days 4 and 8, the band corresponding to the C/EBP-alpha/DNA complex

(as determined with supershift assays) was dramatically decreased in the %%%treated%%% extracts in comparison to control extracts. In contrast, a band corresponding to a C/EBP-beta/DNA complex was found to be enriched
in the %%%treated%%% samples. These data indicate that suppression of differentiation in the 3T3-L1 preadipocyte cell line by TCDD occurs at a short but defined period, during the differentiation program, and involves altered regulation of C/EBP, including the inhibition of C/EBP-alpha.

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19/3,AB/19 (Item 19 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10433476 BIOSIS NO.: 199699054621
Physical and functional association between GADD153 and CCAAT/enhancer-binding protein beta during cellular stress.
AUTHOR: Fawcett Timothy W; Eastman Helen B; Martindale Jennifer L; Holbrook
Nikki J(a)
AUTHOR ADDRESS: (a)Gene Expression Aging Section, Natl. Inst. Aging, Gerontol. Res. Cent., 4940 Eastern Ave., Box 3**USA
JOURNAL: Journal of Biological Chemistry 271 (24):p14285-14289 %%%1996%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: GADD153, a ubiquitously expressed member of the CCAAT/enhancer-
%%%binding%%% %%%protein%%% (%%%C%%%/EBP) family is induced by a wide
variety of growth-arresting and DNA-damaging agents. Functionally, GADD153 has been postulated to act as a dominant-negative regulator of C/EBPs. Therefore we sought to gain evidence for interactions between GADD153 and other C/EBPs during cellular responses to stress. In this report we have demonstrated that %%%treatment%%% of rat pheochromocytoma
PC12 cells with sodium arsenite leads to enhanced expression of C/EBP-beta and GADD153 (growth arrest and DNA damage inducible gene 153)
but not other C/EBPs. Coimmunoprecipitation experiments provided evidence
for the formation of endogenous GADD153-C/EBP-beta complexes in arsenite-
%%%treated%%% cells. Additional experiments were performed to determine
the role of such complexes in regulating GADD153 expression. Previous studies in our laboratory demonstrated that the GADD153 promoter contains
a C/EBP binding site through which other C/EBPs interact to transactivate GADD153 expression in liver hepatoma cells. Here, we demonstrate that extracts prepared from arsenite-%%%treated%%% PC12 cells likewise show
increased amounts of factors capable of binding to the GADD153-C/EBP site
and that these complexes are comprised at least in part of C/EBP-beta. Forced expression of C/EBP-beta was found to be capable of transactivating the GADD153 promoter in PC12 cells cotransfected with plasmids expressing a GADD153 reporter gene and C/EBP-beta protein. However, overexpression of GADD153 inhibited the transactivation of the GADD153 promoter by C/EBP-beta. These findings provide evidence for an autoregulatory loop in which stress-induced GADD153 feeds back to attenuate GADD153 expression during the cellular response to stress.

%%%1996%%%

19/3,AB/20 (Item 20 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10246634 BIOSIS NO.: 199698701552
Role of the C terminus in antigen P1 surface localization in Streptococcus mutans and two related cocci.
AUTHOR: Homonylo-Mcgavin Mary K; Lee Song F(a)
AUTHOR ADDRESS: (a)Dep. Appl. Oral Sci., Fac. Dent., Dalhousie Univ., Halifax, NS B3H 3J5**Canada
JOURNAL: Journal of Bacteriology 178 (3):p801-807 %%%1996%%%
ISSN: 0021-9193
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The C terminus of the major surface protein P1 from Streptococcus
mutans is composed of a hydrophilic domain, an LPNTGV motif, a hydrophobic domain, and a charged tail. These features are shared by surface proteins from many gram-positive coccal bacteria. To investigate the role of the C-terminal domains in antigen P1 surface localization, full-length and truncated P1 gene constructs, which were expressed on the shuttle vector pDL276, were transformed into the P1-negative mutant S. mutans SM3352, Streptococcus gordonii DL-1 and Enterococcus faecalis UV202. Transformants were tested for expression of P1 by enzyme-linked immunosorbent assaying and Western blotting. The results showed that full-length P1 was expressed by transformants of all three bacteria and was localized on the cell surface. A fusion protein composed of the Staphylococcus aureus fibronectin %%%binding%%% %%%protein%%% %%%C%%%
terminus and the P1 protein N terminus was found to surface localize in S. mutans. Deletion of the entire C-terminal domains resulted in P1 being expressed in the culture supernatant. A P1 truncation, which carried only the hydrophilic domain at its C terminus, was found partially associated with the cell surface. This truncated P1 was readily removed from the isolated cell wall by hot sodium dodecyl sulfate-mercaptoethanol extraction. In contrast, the full-length P1 remained associated with the isolated cell wall after similar %%%treatment%%%, suggesting covalent linkages between the full-length P1 and the cell wall. The results described above showed that antigen P1 was anchored to the cell wall by its C-terminal domains probably via covalent linkages with the cell wall. The results also support a universal mechanism involving the C-terminal domains for protein surface localization among this group of gram-positive bacteria.

%%%1996%%%

19/3,AB/21 (Item 21 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10224408 BIOSIS NO.: 199698679326
Transcriptional regulation of the CYP2B1 and CYP2B2 genes by C/EBP-related
proteins.
AUTHOR: Luc Phuong-Van T; Adesnik Milton; Ganguly Sabya; Shaw Peter M(a)
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53711**USA
JOURNAL: Biochemical Pharmacology 51 (3):p345-356 %%%1996%%%
ISSN: 0006-2952
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Cytochrome P450 (CYP) 2B1 and 2B2 are encoded by two closely
related genes, CYP2B1 and CYP2B2, that are expressed at low levels in adult rat liver but are induced markedly by the administration of the drug phenobarbital (PB) or other structurally unrelated hydrophobic compounds to animals. Very little is understood about the molecular mechanisms that control both basal and induced transcription of these genes. We have identified two liver specific DNase I hypersensitive sites associated with the CYP2B1 and CYP2B2 (CYP2B) genes. One site, which maps
to a region in the 5'-flanking region between -2.2 and -2.3 kb, became more resistant to DNase I cleavage in nuclei from PB-%%%treated%%% rats;
the converse was true of the other hypersensitive site, which maps to the proximal promoter region between -0.05 and -0.15 kb. DNase I footprint analysis revealed three prominent and one weak footprinted regions in the

promoter region in the vicinity of the proximal hypersensitive site. Using competitor oligonucleotides, we determined that one footprinted region (FT2), between -42 and -66 bp, is likely to represent a binding sire for CCAATT enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) family members. Indeed, bacterial expressed recombinant C/EBP-alpha bound at this site and formed a footprint pattern identical to the pattern observed with liver nuclear extract. In vitro transcription assays demonstrated that the FT2 site contributed strongly to promoter activity, since its mutation reduced transcription by 80%. Two other sites identified by footprint analysis (FT1 and FT3) are also required to maintain high basal transcription of CYP2B2 promoter constructs in an in vitro transcription assay. Transient transfection experiments confirmed the expectation that C/EBP-alpha could activate the 1.4 kb CYP2B promoter constructs, with mutation of the FT2 site impairing both basal transcription and transactivation by exogenous C/EBPC-alpha.

%%%1996%%%

19/3,AB/22 (Item 22 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10188123 BIOSIS NO.: 199698643041
%%%Binding%%% of activated %%%protein%%% %%%C%%% to a specific receptor on human mononuclear phagocytes inhibits intracellular calcium signaling and monocyte-dependent proliferative responses.
AUTHOR: Hancock Wayne H(a); Grey Shane T; Hau Lena; Akalin Enver; Orthner Carolyn; Sayegh Mohamed H; Salem Hatem H
AUTHOR ADDRESS: (a)Sandoz Cent. Immunobiol., New England Deaconess Hosp., Harvard Med. Sch., 99 Brookline Ave., Bos**USA
JOURNAL: Transplantation (Baltimore) 60 (12):p1525-1532 %%%1995%%%
ISSN: 0041-1337
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Upon activation, mononuclear phagocytes (M-vphi) play key roles in the development of septic shock and multiple host immune responses, but details of the regulation of M-vphi activation are little understood. We recently showed that the physiologic anticoagulant molecule, activated protein C (APC), blocks responses of human blood M-vphi, alveolar M-vphi, or THP-1 cells induced by LPS, IFN-gamma, or PMA, including TNF-alpha production and down-regulation of several LPS binding-related proteins. We now report a possible mechanism of action through inhibition of the rapid intracellular calcium signaling that occurs at the onset of M-vphi activation, and characterization of a specific M-vphi receptor for APC. Flow cytometry studies using Fluo-3 showed that M-vphi activation by Fc-receptor cross-linking or rIFN-gamma caused a rapid increase in free intracellular calcium, a primary event in multiple signal transduction pathways, which was blocked by pretreatment with APC. Consistent with this, addition of APC inhibited PHA-induced T cell proliferation in a dose- and time-dependent manner. Peak suppression (gt 70%) required addition of APC within the first hour of 72 hr cocultures of M-vphi and lymphocytes, and proliferative responses were not restored by addition of IL-2 or TNF-alpha. Biochemical studies showed that 125I-labeled APC bound specifically to M-vphi in a time-dependent and saturable manner. Scatchard analysis indicated there were 180,690 binding sites for APC per cell, which were of high affinity (Kd value of 12.9 nM). Binding of 125I-APC was doubled by activation of M-vphi with LPS, and bound APC was not displaced by the zymogen, protein C (PC), or by enzymatically inactive (diisopropyl fluorophosphate- or PPACK-%%%treated%%%) APC, indicating an absolute requirement for the active site of APC in its binding to M-vphi. APC binding was blocked by a polyclonal Ab to human PC/APC, but not by protein S, factor Va or Xa, or a polyclonal antithrombomodulin antibody. When 125I-APC was crosslinked to its receptor, immunoprecipitated and analyzed by SDS-PAGE under reducing conditions, a covalent complex (110-115 kD) of 125I-ApC (62 kD) and its receptor was seen. In addition, a MO membrane protein of 50-55 kD, as determined by SDS-PAGE, was affinity-purified using an APC-Affigel column, and confirmed by ligand binding. Taken together, our findings document the presence of a M-vphi surface receptor for APC, which appears distinct from a recently described endothelial receptor for PC and APC, and which may be involved in the inhibitory effects of APC on activation of human M-vphi, including M-vphi-dependent T cell proliferation.

%%%1995%%%

19/3,AB/23 (Item 23 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
(c) 2001 BIOSIS. All rts. reserv.

10156425 BIOSIS NO.: 199698611343
Recombinant human soluble thrombomodulin reduces endotoxin-induced pulmonary vascular injury via protein C activation in rats.
AUTHOR: Uchiba Mitsuhiro; Okajima Kenji(a); Murakami Kazunori; Nawa Katsuhico; Okabe Hiroaki; Takatsuki Kiyoshi
AUTHOR ADDRESS: (a)Dep. Lab. Med., Kumamoto Univ. Med. Sch., Honjo 1-1-1, Kumamoto 860**Japan
JOURNAL: Thrombosis and Haemostasis 74 (5):p1265-1270 %%%1995%%%
ISSN: 0340-6245
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Adult respiratory distress syndrome (ARDS) is a serious complication of disseminated intravascular coagulation (DIC) or multiple organ failure. To determine whether recombinant soluble human thrombomodulin (rsTM) may be useful in %%%treating%%% ARDS due to sepsis, we investigated the effect of rsTM on lipopolysaccharide (LPS)-induced pulmonary vascular injury in rats. The intravenous administration of rsTM prevented the increase in pulmonary vascular permeability induced by LPS. Neither heparin Plus antithrombin III (AT III) nor dansyl Glu Gly Arg chloromethyl ketone-%%%treated%%% factor Xa (DEGR-Xa), a selective inhibitor of thrombin generation prevented LPS-induced vascular injury. The agents rsTM, heparin plus AT III, and DEGR-Xa all significantly inhibited the LPS-induced intravascular coagulation. Recombinant soluble TM pretreated with a monoclonal antibody (moAb) that inhibits protein C activation by rsTM did not prevent the LPS-induced vascular injury; in contrast, rsTM pretreated with a moAb that does not affect thrombin %%%binding%%% or %%%protein%%% %%%C%%% activation by rsTM prevented vascular injury. Administration of activated protein C (APC) also prevented vascular injury. LPS-induced pulmonary vascular injury was significantly reduced in rats with leukopenia induced by nitrogen mustard and by ONO-5046, a potent inhibitor of granulocyte elastase. Results suggest that rsTM prevents LPS-induced pulmonary vascular injury via protein C activation and that the APC-induced prevention of vascular injury is independent of its anticoagulant activity, but dependent on its ability to inhibit leukocyte activation.

%%%1995%%%

19/3,AB/24 (Item 24 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10070607 BIOSIS NO.: 199598525525
Induction of heme oxygenase-1 gene expression by lipopolysaccharide is mediated by AP-1 activation.
AUTHOR: Camhi Sharon L; Alam Jawed; Otterbein Leo; Sylvester Sherrie L; Choi Augustine M K(a)
AUTHOR ADDRESS: (a)Div. Pulmonary and Critical Care, Johns Hopkins Univ. Sch. Med., Ross Res. Building, Room 858, 7**USA
JOURNAL: American Journal of Respiratory Cell and Molecular Biology 13 (4):p387-398 %%%1995%%%
ISSN: 1044-1549

DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Gram-negative sepsis is the most common cause of the adult respiratory distress syndrome (ARDS). Lipopolysaccharide (LPS) when administered in vivo produces pathophysiologic changes similar to those seen in ARDS. The pathogenesis of these changes is mediated in part by oxidative stress. We demonstrate that LPS induces high mRNA levels of the stress-inducible gene heme oxygenase-1 (HO-1) in the rat lung. Increased HO-1 mRNA levels correlate with increased HO-1 protein and enzyme activity. Immunohistochemical analyses of lung tissues from rats %%%treated%%% with LPS reveal abundant HO-1 expression in inflammatory and bronchoalveolar epithelial cells. We further examined the molecular regulation of HO-1 gene expression after exposure of RAW 264.7 macrophage cells to LPS in vitro. These cells respond to LPS with increased HO-1 mRNA expression and HO-1 gene transcription. Transcriptional activation of the mouse HO-1 gene by LPS is mediated by a 5' distal enhancer fragment located approximately 4 kbp upstream from the transcription site. Electrophoretic mobility shift assays show increased activator protein-1 (AP-1) binding activity in RAW 264.7 cells after LPS %%%treatment%%%. Mutation of the AP-1 binding site in this enhancer fragment completely abolishes HO-1 gene activation while mutation of CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%/EBP) %%%binding%%% site exerts negligible effect, suggesting that the AP-1 family of transcription factors plays a critical role in regulating HO-1 gene activation following LPS %%%treatment%%%. Furthermore, upstream phosphorylation events modulate this AP-1-dependent expression of the HO-1 gene after LPS %%%treatment%%%.

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19/3,AB/25 (Item 25 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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10012764 BIOSIS NO.: 199598467682
Developmentally and hormonally regulated CCAAT/enhancer-binding protein isoforms influence beta-casein gene expression.
AUTHOR: Raught Brian(a); Liao Warren S-L; Rosen Jeffrey M(a)
AUTHOR ADDRESS: (a)Dep. Cell Biol., Baylor Coll. Med., Houston, TX 77030**
USA
JOURNAL: Molecular Endocrinology 9 (9):p1223-1232 %%%1995%%%
ISSN: 0888-8809
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A highly conserved CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%/EBP)-%%%binding%%% site centered around -134 relative to the transcription start site in the rat beta-casein gene promoter is capable of interacting specifically with recombinant and mammary gland C/EBP proteins. Western blot analysis indicates that C/EBP levels change dramatically throughout mammary gland development. C/EBP-alpha expression is barely detectable in mammary glands from virgin and pregnant animals but is expressed at high levels during lactation and at lower levels during involution. The expression of three C/EBP-beta isoforms (the liver-enriched activating proteins (LAPs); and the liver-enriched inhibiting protein (LIP)) is elevated throughout pregnancy, with LIP expression increasing more than 100-fold. Thus, during pregnancy, a low LAP/LIP ratio (lt 5) is maintained. C/EBP-beta expression decreases at parturition, with LIP diminishing to levels observed in the virgin gland. Therefore, during lactation a more than 100-fold increase in the LAP/LIP ratio is observed. %%%Treatment%%% of the HC11 mammary epithelial cell line with hydrocortisone results in a 10- to 20-fold inhibition of LIP expression, with only minor changes in LAP levels. Therefore, glucocorticoids may impinge upon beta-casein gene expression by altering the ratio of the inhibitory to the activating isoforms of C/EBP-beta. Several previously defined casein gene promoter regions capable of conferring hormone and extracellular matrix inducibility to reporter genes in mammary cells are suggested to be composite response elements, containing putative binding sites for the same set of hormonally and developmentally regulated factors: C/EBP, MGF/Stat5, and the glucocorticoid receptor.

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19/3,AB/26 (Item 26 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09734314 BIOSIS NO.: 199598189232
Expression of the liver-enriched transcription factors C/EBP-alpha, C/EBP-beta, HNF-1, and HNF-4 in preneoplastic nodules and hepatocellular carcinoma in rat liver.
AUTHOR: Flodby Per; Liao De-Zhong; Blanck Agneta; Xanthopoulos Kleanthis G
H; Hallstrom Inger Porsch(a)
AUTHOR ADDRESS: (a)Dep. Med. Nutrition, Huddinge Univ. Hosp., F60 NOVUM,
141 86 Huddinge**Sweden
JOURNAL: Molecular Carcinogenesis 12 (2):p103-109 %%%1995%%%
ISSN: 0899-1987
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The expression patterns of the liver-enriched transcription factors CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%/EBP) alpha and beta and hepatocyte nuclear factor (HNF)-1 and HNF-4 were studied in liver nodules and hepatocellular carcinomas from male rats %%%treated%%% according to the resistant hepatocyte (RH) model. C/EBP-alpha expression was lower at the transcriptional, mRNA, and protein levels in persistent nodules than in the respective surrounding livers. Expression was further decreased in the tumors. Transcriptional downregulation of C/EBP-alpha gene expression was observed already in very early nodules, isolated 3 wk after partial hepatectomy in the RH model. However, no detectable changes were observed in preneoplastic nodules in the transcription or in steady-state mRNA levels of C/EBP-beta, HNF-1, and HNF-4. A slight decrease in C/EBP-beta protein and a more pronounced attenuation of HNF-1 and HNF-4 levels was observed in nodules, being 67%, 37%, and 46% of the levels in the corresponding surrounding livers, respectively. In conclusion, differential regulation of several transcription factors that are associated with the maintenance of the differentiated state of the hepatocytes was observed in preneoplastic and neoplastic liver lesions. This could have an impact on the regulation of a wide array of genes during liver carcinogenesis. Furthermore, the attenuation of C/EBP-alpha expression, regarded as a negative growth regulator, could contribute to the proliferative advantage of nodules during liver carcinogenesis.

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19/3,AB/27 (Item 27 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09666743 BIOSIS NO.: 199598121661
Insulin regulates transcription of the CCAAT/Enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) alpha, beta, and delta genes in fully-differentiated 3T3-L1 adipocytes.
AUTHOR: MacDougald Ormond A; Cornelius Peter; Liu Raymond; Lane M Daniel(a)
AUTHOR ADDRESS: (a)Dep. Biol. Chem., Johns Hopkins Univ., Sch. Med., 725 N.
Wolfe St., Baltimore, MD 21205**USA
JOURNAL: Journal of Biological Chemistry 270 (2):p647-654 %%%1995%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: The effect of insulin on expression of CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) alpha, beta, and delta was
investigated in fully-differentiated 3T3-L1 adipocytes. %%%Treatment%%% of adipocytes with insulin stimulated rapid dephosphorylation of C/EBP-alpha, and repressed the expression of C/EBP-alpha within 2-4 h, with gt 90% suppression occurring at 24 h. While insulin induced expression of C/EBP-beta and C/EBP-delta within 1 h and caused a gt 20-fold increase by 4 h, expression returned to nearly pretreatment levels by 24 h. The insulin concentration dependence of these effects was consistent with involvement of the insulin receptor. Gel shift analysis revealed that 6 h of insulin %%%treatment%%% decreased the binding of nuclear C/EBP-alpha while increasing binding of nuclear C/EBP-beta and C/EBP-delta. The reciprocal effects of insulin on the steady-state levels of C/EBP transcription factors can be accounted for kinetically and quantitatively by changes in their mRNA levels, which can be accounted for by effects on gene transcription. The effects of insulin on adipocyte gene transcription (e.g. GLUT4) may be mediated, at least in part, by down-regulation of C/EBP-alpha and/or its dephosphorylation.

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19/3,AB/28 (Item 28 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09641486 BIOSIS NO.: 199598096404
Hepatic CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP-alpha and
C/EBP-beta) expression changes with riboflavin deficiency, diet restriction and starvation in rats.
AUTHOR: Chapin Rebecca B; Brady Paul S; Barke Roderick A; Brady Linda J(a)
AUTHOR ADDRESS: (a)Dep. Food Sci. Nutr., Univ. Minn., St. Paul, MN 55108**
USA
JOURNAL: Journal of Nutrition 124 (12):p2365-2375 %%%1994%%%
ISSN: 0022-3166
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: To study the role of nuclear regulatory proteins in mediating dietary effects, hepatic CCAAT/enhancer %%%binding%%% %%%protein%%% (
%%%C%%%/EBP), mRNA and transcription rate were measured for C/EBP-alpha
and C/EBP-beta in nutritional states that profoundly alter energy metabolism and growth. Weanling male Sprague-Dawley rats were fed riboflavin-sufficient (R+) or deficient (R-) diets for 4 wk. A diet-restricted, pair-fed (RP) group was maintained concurrently, because riboflavin-deficient rats voluntarily decrease food consumption by apprx 50% compared with controls. Half of each group was deprived of food for 48 h. The 4-wk %%%treatment%%% altered hepatic levels of both proteins (P
lt 0.05). C/EBP-alpha protein levels were increased apprx twofold by diet restriction. C/EBP-beta protein levels were increased nearly threefold by riboflavin deficiency. Starvation had no significant effect on the expression of either protein. We investigated the mechanism responsible for increased protein by measuring steady-state mRNA levels and transcription rates for C/EBP-alpha and C/EBP-beta. In both isoforms, increases in mRNA were parallel to increases in transcription rates. The nutrient-induced changes in protein, mRNA and transcription rates could not be attributed only to alterations in serum glucagon or insulin concentrations. We conclude that 1) C/EBP-alpha and C/EBP-beta expression
responds to diet but may involve different dietary signals for diet restriction vs. riboflavin deficiency; 2) the dietary regulation of C/EBP-alpha and C/EBP-beta expression seems to be controlled in part at the level of gene transcription; and 3) C/EBP-alpha and C/EBP-beta nuclear proteins, by virtue of their increased quantities, may participate in regulating altered energy metabolism and growth by influencing hepatic transcription of key metabolic enzymes.

%%%1994%%%

19/3,AB/29 (Item 29 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09544469 BIOSIS NO.: 199497552839
Multiple elements within the 5' distal enhancer of the mouse heme oxygenase-1 gene mediate induction by heavy metals.
AUTHOR: Alam Jawed
AUTHOR ADDRESS: Dep. Mol. Genetics, Alton Ochsner Med. Foundation, 1516
Jefferson Highway, New Orleans, LA 70121**USA
JOURNAL: Journal of Biological Chemistry 269 (40):p25049-25056 %%%1994%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: A 268-base pair 5' distal fragment, SX2, which mediates basal level and inducer-dependent activation of the mouse heme oxygenase-1 gene, contains two activator protein-1 (AP-1) binding sites (Alam, J., and Zhining, D. (1992) J. Biol. Chem. 267,21894-21900). Mutation of both AP-1 binding elements diminishes (by 50-70%), but does not abolish, the enhancer activity of SX2 in transient expression assays, suggesting that other sequences contribute to enhancer function. Directly upstream of the AP-1 binding sites are two copies of a sequence motif, TGAGGAAAT, which
resemble elements found in cellular and viral genes that are known to interact with the CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%
/EBP) family of transcription factors. These SX2 sequences bind specifically to liver-enriched, heat-stable nuclear proteins and confer C/EBP alpha-dependent transactivation of the heterologous chloamphenicol acetyltransferase (CAT) gene. Site-directed mutagenesis of these 9-base pair elements abolishes protein binding and transactivation, establishing these sequences as functional C/EBP binding sites. Stably transfected SX2/CAT fusion genes are induced between 37- and 44-fold in mouse hepatoma, Hepa, cells and between 52- and 111-fold in mouse fibroblast L929 cells in response to CdCl-2 %%%treatment%%%. Subfragments of SX2
lacking the AP-1 binding elements do not mediate cadmium-dependent activation of the CAT gene, whereas subfragments containing the AP-1 binding elements, but lacking the C/EBP binding sites, exhibit only partial transcriptional activity. Site-directed mutagenesis of one or more of the C/EBP and AP-1 binding sites indicates that each of them elements is required for optimal activity of the SX2 enhancer fragment. The AP-1 binding elements, however, appear to be more important for induction as constructs containing multiple copies of either of the AP-1 binding elements, but not the C/EBP binding sequences, are readily activated by CdCl-2. %%%Treatment%%% of Hepa cells with cadmium or home
does not alter the nuclear concentration of AP-1 or C/EBP binding activity.

%%%1994%%%

19/3,AB/30 (Item 30 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09409800 BIOSIS NO.: 199497418170
Induction of GADD153, A CCAAT/Enhancer-%%%binding%%% %%%Protein%%% (%%%C%%%
/EBP)-related Gene, during the Acute Phase Response in Rats: Evidence for the involvement of C/EBPs in regulating its expression.
AUTHOR: Sylvester Sherrie; Ap Rhys Colette M J; Luethy-Martindale Jennifer
D; Holbrook Nikki J(a)
AUTHOR ADDRESS: (a)Sect. Gene Expression Aging, Gerontol. Res. Cent., Natl.
Inst. Aging, Baltimore, MD 21224**USA
JOURNAL: Journal of Biological Chemistry 269 (31):p20119-20125 %%%1994%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: CCAAT/enhancer-binding proteins (C/EBPs) comprise a homologous
group of transcriptional regulators that control liver and fat differentiation and are involved in regulating the expression of acute phase reactants during the host response to inflammation. GADD153, a unique member of the C/EBP family, has been proposed to act as a dominant
negative inhibitor of other C/EBPs, but little is known about its expression in liver or its role in the processes described above. We have examined its expression during the acute phase response (APR) and have shown that)like C/EBP-beta and C/EBP-delta, GADD153 mRNA is markedly
induced in livers of rats %%%treated%%% with lipopolysaccharide to initiate the APR. Interestingly, its induction is temporally delayed relative to that of C/EBP-beta and C/EBP-delta but is similar to that of acute phase reactants shown to be regulated by C/EBPs. Footprint analysis of the GADD153 promoter showed binding of proteins in liver extracts of both untreated and lipopolysaccharide-injected rats to a putative C/EBP regulatory site. Gel shift analysis showed that although present constitutively, binding activity was increased in extracts from lipopolysaccharide-%%%treated%%% animals. Both C/EBP-alpha and C/EBP-beta
were shown to contribute to the binding activity with the contribution by C/EBP-beta increasing during the APR. Support for the functional role of this C/EBP-binding site and its interaction with C/EBPs in regulating GADD153 expression was obtained with cultured HepG2 hepatoma cells in which overexpression of C/EBP-beta was found to transactivate expression of a plasmid containing the GADD153 promoter linked to a reporter gene. These findings suggest that the GADD153 gene is itself regulated by C/EBPs during the host response to inflammation and that GADD153 is likely to contribute to the regulation of other genes whose expression is altered during the APR.
%%%1994%%%

19/3,AB/31 (Item 31 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09405887 BIOSIS NO.: 199497414257
Glucocorticoids reciprocally regulate expression of the CCAAT/enhancer-binding protein alpha and delta genes in 3T3-L1 adipocytes
and white adipose tissue.
AUTHOR: MacDougald Ormond A; Cornelius Peter; Lin Fang-Tsyr; Chen Sylvia S;
Lane M Daniel(a)
AUTHOR ADDRESS: (a)Dep. Biological Chemistry, Johns Hopkins Univ. Sch.
Med., Baltimore, MD 21205**USA
JOURNAL: Journal of Biological Chemistry 269 (29):p19041-19047 %%%1994%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Glucocorticoid agonists, i.e. dexamethasone or triamcinolone acetonide, rapidly induce expression of
CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%/EBP) delta and repress expression of C/EBP-alpha
in fully differentiated 3T3-L1 adipocytes. Within 30 min of glucocorticoid %%%treatment%%%, the cellular level of C/EBP-delta rises dramatically, increasing gt 100-fold within 6 h. Concurrently, the level of C/EBP-alpha decreases, reaching a minimum within 4 h. The dexamethasone concentration dependence and steroid specificity of these responses suggest that both processes are mediated by the glucocorticoid receptor. The reciprocal effects of dexamethasone on the steady-state levels of C/EBP-alpha and C/EBP-delta can be accounted for kinetically and quantitatively by changes in their mRNA levels and by the transcription rates of their respective genes. The glucocorticoid-induced changes in expression of the C/EBP isoforms are correlated with the transcriptional activation of the SCD1 gene, an adipocyte gene known to be transactivated by C/EBP isoforms. Glucocorticoids also regulate expression of the C/EBP isoforms in vivo. Within 4 h of administration of dexamethasone or triamcinolone acetonide to adult rats, expression of C/EBP-delta is induced in white adipose tissue while expression of C/EBP-alpha is repressed. Like the response in 3T3-L1 adipocytes, the effects of dexamethasone on C/EBP-alpha in white adipose tissue are rapid and transient.

%%%1994%%%

19/3,AB/32 (Item 32 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09307646 BIOSIS NO.: 199497316016
%%%Binding%%% of urinary %%%protein%%% %%%C%%% inhibitor to cultured human
epithelial kidney tumor cells (TCL-598): The role of glycosaminoglycans present on the luminal cell surface.
AUTHOR: Priglinger Ute; Geiger Margarethe(a); Bielek Edith; Vanyek Erika;
Binder Bernd R
AUTHOR ADDRESS: (a)Lab. Clinical Experimental Physiol., Dep. Med. Physiol.,
Schwarzspanierstrasse 17, A1090 Vienna**Austria
JOURNAL: Journal of Biological Chemistry 269 (20):p14705-14710 %%%1994%%%
ISSN: 0021-9258
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: %%%Binding%%% of urinary %%%protein%%% %%%C%%% inhibitor (PCI) to
cultured human epithelial kidney tumor cells (TCL-598) was studied. Binding was dose-dependent, time-dependent, and saturable. Heparin interfered in a dose-dependent way with PCI binding to TCL-598 as did heparan sulfate and to a lesser degree also dermatan sulfate. Pretreatment of TCL-598 with protamine sulfate inhibited subsequent binding of PCI in a dose-dependent manner and gt 100 mu-g/ml protamine sulfate reduced binding of PCI to lt 10% of the control. Binding of 125I-PCI was specific, and bound 125I-PCI was recovered from the cells by heparin %%%treatment%%% or detached together with intact cells by EDTA
%%%treatment%%%, migrated on sodium dodecyl sulfate-polyacrylamide gel
electrophoresis with the same mobility (M-r = 57,000) as unbound 125I-PCI. Furthermore, cell-bound PCI was functionally active as judged from its ability to inhibit the amidolytic activity of urokinase, and its inhibitory activity was stimulated apprxeq 3-4-fold as compared to fluid-phase PCI. Immunogold electron microscopy revealed that PCI-antigen presented to the cells from the luminal side bound exclusively to that surface in native as well as in prefixed cells. This binding of PCI was abolished in the presence of heparin (50 mu-g/ml) and after pretreatment of the cells either with protamine sulfate (400 mu-g/ml) or with heparinase III (0.5 unit/ml). A slight decrease in PCI binding was seen after pretreatment of the cells with chondroitinase ABC and chondroitinase AC. In contrast, binding of PCI to extracellular matrices of TCL-598 was decreased to apprxeq 70% after chondroitinase ABC %%%treatment%%% of the extracellular matrices, whereas both heparinase III or chondroitinase AC %%%treatment%%% only reduced matrix-bound PCI to
apprxeq 95%. These data suggest that heparan sulfate-containing proteoglycans are predominantly involved in binding of PCI to the luminal side of TCL-598, while dermatan sulfate-containing proteoglycans, the overall predominant PCI-binding proteoglycans in TCL extracts, are responsible for PCI binding to the extracellular matrix. Heparan sulfate, however, exposed to an environment containing PCI under physiological conditions, might localize PCI and modulate its target enzyme specificity in vivo.

%%%1994%%%

19/3,AB/33 (Item 33 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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09304383 BIOSIS NO.: 199497312753
Serum amyloid A gene expression under acute-phase conditions involves participation of inducible C/EBP-beta and C/EBP-delta and their

activation by phosphorylation.
AUTHOR: Ray Alpana; Ray Bimal K(a)
AUTHOR ADDRESS: (a)Dep. Vet Microbiol., University Missouri, 20 Connaway
Hall, Columbia, MO 65211**USA
JOURNAL: Molecular and Cellular Biology 14 (6):p4324-4332 %%%1994%%%
ISSN: 0270-7306
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: Serum amyloid A (SAA) is a plasma protein whose synthesis is markedly increased in the liver during the inflammatory process. Previous analysis of SAA promoter function implicated the involvement of the CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%/EBP) in controlling this process. In this study, using antibodies against three C/EBP isoforms in DNA-binding and Western blot (immunoblot) assays, we found that in response to inflammatory signals, both C/EBP-delta and C/EBP-beta are induced and that their interactions with the SAA promoter element are necessary for the increased SAA gene expression. Cotransfections of liver cells with an SAA promoter-linked reporter chloramphenicol acetyltransferase gene and murine sarcoma virus-expressed C/EBP-delta or C/EBP-beta confirm such phenomena. The increased transactivating ability in the presence of the cellular phosphatase inhibitors okadaic acid and sodium orthovanadate, coupled with the observation that dephosphorylation severely inhibits the DNA-binding ability in vitro, implicates a role of phosphorylation in the regulation of the activities of the C/EBP-delta isoform. Consistent with these findings, we have detected higher levels of DNA-binding activity of C/EBP-delta prepared from cells %%%treated%%% with phosphatase inhibitors. We also present evidence that C/EBP-delta is a phosphoprotein. These results suggest that C/EBP-delta is regulated by phosphorylation and, in conjunction with C/EBP-beta, is one of the major proteins responsible for the increased transcription of the SAA gene in response to inflammatory stimuli.

%%%1994%%%

19/3,AB/34 (Item 34 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08853036 BIOSIS NO.: 199396004537
Participation of the transcription factor C/EBP-delta in the acute-phase regulation of the human gene for complement component C3.
AUTHOR: Juan Todd S-C; Wilson Deborah R; Wilde Margaret D; Darlington Gretchen J(a)
AUTHOR ADDRESS: (a)Dep. Pathol., Baylor Coll. Med., One Baylor Plaza, Houston, TX 77030**USA
JOURNAL: Proceedings of the National Academy of Sciences of the United States of America 90 (7):p2584-2588 %%%1993%%%
ISSN: 0027-8424
DOCUMENT TYPE: Article
RECORD TYPE: Abstract
LANGUAGE: English

ABSTRACT: C3, the third component of complement, is critical in the host immune response in that it is involved in both the classical and alternative pathways of complement activation. We have previously shown that a region (bp -127 to -70) within the C3 promoter is indispensable for conferring interleukin 1 (IL-1) responsiveness to this gene. A sequence comparison reveals two CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) consensus sequences, basic DNA binding region and leucine zippers 1 and 2 (bZIP1 and bZIP2), within this region. Site-directed mutagenesis of the more 3' C/EBP site (bZIP1) in the C3 promoter significantly reduced the basal level of expression and the IL-1 responsiveness of the reporter gene, whereas mutation in the second, more 5', C/EBP consensus sequence (bZIP2) had a minimal effect on basal expression and IL-1 inducibility. Electrophoretic-mobility-shift assays, with and without antibodies to the different C/EBP proteins that "supershift" protein-DNA complexes, demonstrated that proteins binding at the 3' C/EBP site formed several complexes. Antibodies to C/EBP-alpha supershifted the majority of complexes formed with extracts from control cells. Antibodies directed against C/EBP-delta supershifted the major IL-1-inducible complexes. Western immunoblot analyses showed that the level of C/EBP-delta protein was increased dramatically in the nuclei of Hep 3B2 cells after 4 h of IL-1 %%%treatment%%%. When Hep 3B2 cells were cotransfected with a C/EBP-delta expression vector and a construct with a C3 promoter and a reporter gene, C/EBP-delta was able to transactivate the C3 promoter in an IL-1-responsive manner. The data strongly suggest that C/EBP-delta is the major protein responsible for regulating the acute-phase expression of the human C3 gene.

%%%1993%%%

19/3,AB/35 (Item 35 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08424528 BIOSIS NO.: 000094131732
CALCIUM IONOPHORE A23187 INDUCES EXPRESSION OF THE GROWTH ARREST AND DNA DAMAGE INDUCIBLE CCAAT-ENHANCER-%%%BINDING%%% %%%PROTEIN%%% %%%C%%% -EBP-RELATED GENE GADD153 CALCIUM INCREASES TRANSCRIPTIONAL ACTIVITY AND MRNA STABILITY
AUTHOR: BARTLETT J D; LUETHY J D; CARLSON S G; SOLLOTT S J; HOLBROOK N J
AUTHOR ADDRESS: LABORATORY MOLECULAR GENETICS, NATIONAL INSTITUTE AGING, BALTIMORE, MD. 21224.
JOURNAL: J BIOL CHEM 267 (28). 1992. 20465-20470. %%%1992%%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: gadd153 is a CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%% /EBP)-related gene whose expression is induced in response to growth arrest and DNA damage. This investigation explored the possibility that Ca2+ might play a role in regulating expression of gadd153. We have demonstrated that %%%treatment%%% of HeLa cells with the calcium ionophores A23187 and ionomycin leads to the induction of gadd153 mRNA. The induction was rapid; increases in mRNA were detected by 90 min of %%%treatment%%%, and near maximum levels were achieved witin 5-h exposure to A23187. Elevated mRNA levels resulted from both an increase in the rate of gadd153 transcription and an increase in the stability of the gadd153 mRNA. The response was not dependent on protein kinase C nor was it coupled to c-fos expression. Buffering intracellular and extracellular Ca2+ by combined %%%treatment%%% with BAPTA-AM (acetoxymethyl ester form of bis(aminophenoxy)ethane N,N'-tetraacetic acid) and EGTA prevented the induction of gadd153 mRNA by A23187. In addition, these %%%treatments%%% prevented the induction of gadd153 mRNA in response to the DNA damaging agent methyl methanesulfonate. We conclude that intracellular Ca2+ plays a role in regulating gadd153 expression. More specifically, Ca2+ likely plays a role in the induction of gadd153 mRNA following DNA damage.

%%%1992%%%

19/3,AB/36 (Item 36 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08422530 BIOSIS NO.: 000094129734
ROLE OF CAAT-ENHANCER BINDING PROTEIN ISOFORMS IN THE CYTOKINE REGULATION OF ACUTE-PHASE PLASMA PROTEIN GENES
AUTHOR: BAUMANN H; MORELLA K K; CAMPOS S P; CAO Z; JAHREIS G P

AUTHOR ADDRESS: DEP. MOLECULAR CELLULAR BIOL., ROSWELL PARK CANCER INST., BUFFALO, NEW YORK 14263.
JOURNAL: J BIOL CHEM 267 (27). 1992. 19744-19751. %%%1992%%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Rat hepatic cells respond to interleukin (IL) -1, IL-6, and dexamethasone %%%treatment%%% by increasing the transcription rate of acute-phase plasma protein genes. The same conditions lead to changes in the expression of CAAT-enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) isoforms which are specific to the hepatic cell line. To identify the relationship between C/EBP isoforms and acute-phase protein gene activation, the hormone-specific expression of C/EBP.alpha., .beta., and .delta. was determined in H-35 and HTC cells and was compared to acute-phase liver. C/EBP.beta. was found to be the principal isoform in hepatoma cells and to be strongly stimulated by cytokines and dexamethasone in H-35 cells. Transactivating functions were observed for all three C/EBP isoforms by contransfection of CAT gene reporter constructs containing cytokine and glucocorticoid response elements of acute-phase protein genes and expression plasmids for mouse C/EBP.alpha., .beta. and .delta. into rat and human hepatoma cells. The degree of C/EBP-mediated transactivation was, however, extremely variable among the different regulatory elements. Transcription run-on reactions with nuclei from transiently transfected H-35 indicated that cotransfected C/EPB.beta. increases basal expression of reporter gene constructs as well as the dexamethasone-mediated stimulation of constructs containing the glucocorticoid response elements of the rat .alpha.1-acid glycoprotein gene, but did not accelerate or enhance hormone-dependent transcription activation of reporter gene plasmids containing the IL-6 regulatory element of the .beta.-fibrinogen gene. Activation of the reporter gene constructs appeared to be temporally and quantitatively correlated with the amount of nuclear C/EBP as determined by two-dimensional Western and Southwestern blot analyses.

%%%1992%%%

19/3,AB/37 (Item 37 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08333333 BIOSIS NO.: 000094084581
CCAAT-ENHANCER BINDING PROTEIN EXPRESSION IS RAPIDLY EXTINGUISHED IN TA1 ADIPOCYTE CELLS %%%TREATED%%% WITH TUMOR NECROSIS FACTOR
AUTHOR: WILLIAMS P M; CHANG D J; DANESCH U; RINGOLD G M; HELLER R A
AUTHOR ADDRESS: INST. CANCER AND DEV. BIOL., SYNTEX RES., 3401 HILLVIEW AVE., PALO ALTO, CALIF. 94303.
JOURNAL: MOL ENDOCRINOL 6 (7). 1992. 1135-1141. %%%1992%%%
FULL JOURNAL NAME: Molecular Endocrinology
CODEN: MOENE
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Tumor necrosis factor (TNF) has been shown to have diverse effects on a wide variety of cell types. In the mouse adipogenic TA1 cell line, TNF completely abolishes differentiation and reverts fully differentiated fat cells into fibroblasts. This block in differentiation and its reversal is due to the rapid reduction in the expression of adipose-specific genes. This study reports that the transcription factor, CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP), previously reported to promote the differentiation of 3T3-L1 adipocytes, is expressed in TA1 cells. During their growth in culture, the levels of C/EBP, as evidenced by its cellular levels of specific mRNA, protein, and DNA binding activity, increase dramatically when cell reach confluence and proceed to differentiate. Addition of TNF to cultured preadipocytes of fully differentiated adipocytes rapidly reduces C/EBP levels and is accompanied by the decrease in expression of adipose-specific genes. C/EBP binding sites occur in several adipose-specific genes, and here it is demonstrated that its presence in a novel adipose-specific gene, Clone 47, also referred to as FSP27, may be responsible for the strong down-regulation of the expression of the Clone 47 (FSP27) promoter-liked chloramphenicol acetyl transferase gene by TNF. This study proposes that the loss of C/EBP in response to TNF %%%treatment%%% may in part explain the loss of the adipocyte differentiated state.

%%%1992%%%

19/3,AB/38 (Item 38 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08135523 BIOSIS NO.: 000093122671
DIFFERENTIAL EXPRESSION OF THREE C-EBP ISOFORMS IN MULTIPLE TISSUES DURING THE ACUTE PHASE RESPONSE
AUTHOR: ALAM T; AN M R; PAPACONSTANTINOU J
AUTHOR ADDRESS: DEP. HUMAN BIOL. CHEM. GENETICS, 613 BASIC SCI. BUILDING, RT. F43, UNIV. TEXAS MED. BRANCH, GALVESTON, TEXAS 77550.
JOURNAL: J BIOL CHEM 267 (8). 1992. 5021-5024. %%%1992%%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Eucaryotic organisms possess natural defense processes triggered by stress factors such as injury, infection, and inflammation. The acute phase response is an early defense mechanism during which striking changes in protein synthesis occur in the liver and other tissues. The altered expression of many acute phase protein genes is at the transcriptional level. Some of these genes have DNA binding sites for the CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) family of transcription factors. We report here that in vivo expression of three isoforms of C/EBP is dramatically changed during the acute phase response. The steady-state mRNA levels of C/EBP.alpha. decreased significantly in the liver, lung and fat tissues of lipopolysaccharide (LPS)-%%%treated%%% mice; moreover, nuclear run-off transcription assays indicated a decrease in the rate of C/EBP.alpha. gene transcription in isolated liver nuclei. The steady-state levels of C/EBP.beta. and new isoform, C/EBP.delta., were dramatically increased in many tissues within 4 h following LPS %%%treatment%%%. The rates of transcription of these two genes were only minimally altered in liver but significantly increased in kidney nuclei isolated from stimulated animals. Thus, the C/EBP isoforms exhibit differential mechanisms in their responses to LPS in various tissues and are likely to play an important role in mediating the transcriptional activation of genes involved in the acute phase response.

%%%1992%%%

19/3,AB/39 (Item 39 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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08016255 BIOSIS NO.: 000093061178
TUMOR NECROSIS FACTOR-INDUCED REVERSAL OF ADIPOCYTIC PHENOTYPE OF 3T3-L1 CELLS IS PRECEDED BY A LOSS OF NUCLEAR CCAAT-ENHANCER %%%BINDING%%% %%%PROTEIN%%% %%%C%%%-EBP
AUTHOR: RON D; BRASIER A R; MCGEHEE R E JR; HABENER J F
AUTHOR ADDRESS: LAB. MOL. ENDOCRINOL., MASS. GEN. HOSP., HOWARD HUGHES MED. INST., HARVARD MED. SCH., BOSTON, MASS. 02114.
JOURNAL: J CLIN INVEST 89 (1). 1992. 223-233. %%%1992%%%
FULL JOURNAL NAME: Journal of Clinical Investigation
CODEN: JCINA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Tumor necrosis factor (TNF)-%%%treated%%% 3T3-L1 adipocytes were
used as a model for studying the effects of systemic inflammation of adipose tissue. Lipopolysaccharide-%%%treatment%%% monocyte-conditioned
medium or recombinant human TNF.alpha. induced morphological dedifferentiation of the adipocytes and led to loss of adipocyte specific gene expression. Gel shift, Southwestern and Western immunoblot analysis demonstrated that dedifferentiation was preceded by a decrease in DNA binding activity and protein level of the transcription factor CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP). Liver
activating protein, a related protein that binds indentical DNA sequences, increased during cytokine %%%treatment%%%. Both proteins activate specific enhancer elements located in the promotor region of many genes whose transcription is altered during systemic inflammation. Pulse-chase labeling followed by immunoprecipitation demonstrated that C/EBP is a rapidly turning over protein in adipocytes and that cytokine %%%treatment%%% led to a specific, time dependent decrease in its rate of
synthesis. Because C/EBP binding sites have been shown to play an important role in regulating the expression of genes involved in adipocyte metabolism, we propose that the TNF-induced changes in the complement of transcription factors binding those sites may be important in the pathogenesis of inflammation-induced atrophy of adipose tissue.

%%%1992%%%

19/3,AB/40 (Item 40 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07996770 BIOSIS NO.: 000093052443
A PHOSPHORYLATION SITE LOCATED IN THE AMINO-TERMINAL DOMAIN OF C-MYC
INCREASES TRANSACTIVATION OF GENE EXPRESSION
AUTHOR: SETH A; ALVAREZ E; GUPTA S; DAVIS R J
AUTHOR ADDRESS: HOWARD HUGHES MEDICAL INSTITUTE, PROGRAM MOLECULAR
MEDICINE, UNIVERSITY MASSACHUSETTS MEDICAL SCHOOL, 373 PLANTATION ST.,
WORCESTER, MASS. 01605.
JOURNAL: J BIOL CHEM 266 (35). 1991. 23521-23524. %%%1991%%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The c-myc gene encodes a sequence-specific DNA-%%%binding%%%
%%%protein%%% (%%%c%%%-Myc) that forms leucine zipper complexes and can
act as a transcription factor. Growth factor stimulation of cells causes the phosphorylation of the c-Myc transcriptional activation domain at Ser62 within a proline-rich region that is highly conserved among members of the Myc family (Alvarez, E., Northwood, I. C., Gonzalez, F. A., Latour, D. A., Seth, A., Abate, C., Curran, T., and Davis, R. J. (1991) J. Biol. Chem. 266, 15277-15285). This phosphorylation site is a substrate for growth factor-regulated MAP kinases and for the cell cycle-dependent protein kinase p34cdc2. We report that serum %%%treatment%%% of cells results in a marked increase in the transactivation of gene expression mediated by the c-Myc transcriptional activation domain. A point mutant at the site of growth factor-stimulated phosphorylation (Ser62) decreases the serum induction of transactivation. These data indicate that the c-Myc transcriptional activation domain may be a direct target of signal transduction pathways.

%%%1991%%%

19/3,AB/41 (Item 41 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07659780 BIOSIS NO.: 000092017201
NATURAL ANTICOAGULANTS IN SYSTEMIC LUPUS ERYTHEMATOSUS DEFICIENCY OF
PROTEIN S BOUND TO C4BP ASSOCIATED WITH RECENT HISTORY OF VENOUS
THROMBOSES ANTIPHOSPHOLIPID ANTIBODIES AND THE ANTIPHOSPHOLIPID SYNDROME
AUTHOR: RUIZ-ARGUELLES G J; RUIZ-ARGUELLES A; ALARCON-SEGOVIA D; DRENKARD C
; VILLA A; CABIEDES J; PRESNO-BERNAL M; DELEZE M; ORTIZ-LOPEZ R; VAZQUEZ
PRADO J
AUTHOR ADDRESS: DEP. IMMUNOL. AND RHEUMATOL., INST. NACL. NUTRICION
SALVADOR ZUBIRAN, VASCO DE QUIROGA 15, 1400 MEXICO DF, MEXICO.
JOURNAL: J RHEUMATOL 18 (4). 1991. 552-558. %%%1991%%%
FULL JOURNAL NAME: Journal of Rheumatology
CODEN: JRHUA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The association of thrombosis with antiphospholipid antibodies (aPL) in patients with systemic lupus erythematosus (SLE) could be due to their interference with natural phospholipid dependent anticoagulant mechanisms. We studied antigenic protein C (APC), functional protein C (FPC), free protein S (FPS), protein S bound to C4 binding protein (C4bp-S), antithrombin III (ATIII), as well as IgG and IgM anticardiolipin antibodies (aCL) in 38 patients with SLE with a history of thromboses and 70 patients with SLE without such history. We found a high frequency of deficiencies of natural anticoagulants in both groups of patients with SLE but, because of patient selection, we could not determine the actual prevalence of these defects. Patients having had a venous thrombosis in the previous year had low C4bp-S more frequently than patients with older or no thromboses. When we divided our patients with SLE into those who had a definite, probable, questionable or no antiphospholipid syndrome (aPS) we found the frequency of C4bp-S deficiency to be significantly higher in those with definite aPS than in those without aPS. Intermediate proportions were found in patients with probable and questionable aPS. The levels of C4bp-S decreased as the levels of aCL, particularly IgG, increased. Stepwise discriminant analysis of natural anticoagulants selected deficiencies of C4bp-S and EFPC with increased ATIIIas a set of variables with highest predictive power for classification of patients with and without aPS. Thus, deficiencies of natural anticoagulants may occur frequently in patients with SLE. Those of C4bp-S appear to be related to the presence of aPL associated with evidence of aPS and with thromboses that occurred within a year. A triad of low C4bp-S and FPC and high ATIII may serve to discriminate patients with aPS from those without, suggesting in them the presence of a hypercoagulable state.

1991

19/3,AB/42 (Item 42 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

07571044 BIOSIS NO.: 000091111598
MYXOCOCCUS-XANTHUS PROTEIN C IS A MAJOR SPORE SURFACE PROTEIN
AUTHOR: MCCLEARY W R; ESMON B; ZUSMAN D R
AUTHOR ADDRESS: DEP. MOL. CELL BIOL., UNIV. CALIFORNIA, BERKELEY, CALIF.
94720.
JOURNAL: J BACTERIOL 173 (6). 1991. 2141-2145. %%%1991%%%
FULL JOURNAL NAME: Journal of Bacteriology
CODEN: JOBAA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Fruiting body formation in Myxococcus xanthus involves the aggregation of cells to form mounds and the differentiation of rod-shaped cells into spherical myxospores. The surface of the myxospore is composed of several sodium dodecyl sulfate (SDS)-soluble proteins, the best characterized of which is protein S (Mr, 19,000). We have identified a new major spore surface protein called protein C (Mr, 30,000). Protein C is not present in extracts of vegetative cells but appears in extracts of developing cells by 6 h. Protein C, like protein S, is produced during starvation in liquid medium but is not made during glycerol-induced sporulation. Its synthesis is blocked in certain developmental mutants

but not others. When examined by SDS-polyacrylamide gel electrophoresis, two forms of protein C are observed. Protein C is quantitatively released from spores by %%%treatment%%% with 0.1 N NaOH or by boiling in 1% SDS.
It is slowly washed from the spore surface in water but is stabilized by the presence of magnesium. %%%Protein%%% %%%C%%% %%%binds%%% to the
surface of spores depleted of protein C and protein S. Protein C is a useful new marker for development in M. xanthus because it is developmentally regulated, spore associated, abundant, and easily purified.

%%%1991%%%

19/3,AB/43 (Item 43 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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07433212 BIOSIS NO.: 000091039201
A 58-BASE-PAIR REGION OF THE HUMAN C3 GENE CONFERS SYNERGISTIC INDUCIBILITY
BY INTERLEUKIN-1 AND INTERLEUKIN-6
AUTHOR: WILSON D R; JUAN T S-C; WILDE M D; FEY G H; DARLINGTON G J
AUTHOR ADDRESS: DEP. OF PATHOL., BAYLOR COLL. OF MED., HOUSTON, TEXAS
77030.
JOURNAL: MOL CELL BIOL 10 (12). 1990. 6181-6191. %%%1990%%%
FULL JOURNAL NAME: Molecular and Cellular Biology
CODEN: MCEBD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We have cloned the promoter for the human third component of complement (C3) gene and have identified sequences involved in its regulation during the acute-phase response. A construct linking 199 bp of the C3 promoter to the firefly luciferase gene was found to be very responsive to interleukin-1 (IL-1) and modestly responsive to interleukin-6 (IL-6) by transfection analysis in the human hepatoma line Hep3B2. Simultaneous %%%treatment%%% with the two cytokines showed a
strong synergy between the actions of the two molecules. A 58-bp fragment (-127 to -70 bp) was shown by 5' and 3' deletional mutagenesis to contain cis-acting elements that mediated both the IL-1 response and the IL-1-plus-IL-6 synergistic response of this promoter. When coupled to a heterologous promoter, this fragment enabled the synergistic induction by IL-1 plus IL-6. Sequences homologous to the palindrome ACATTGCACAATCT,
which mediates the induction of the IL-6 gene by IL-1 (S. Akira, H. Isshiki, T. Sugita, O. Tanabe, S. Kinoshita, Y. Nishio, T. Nakajima, T. Hirano, and T. Kishimoto, EMBO J. 9:1987-1906, 1990), and the core sequence of the IL-6-responsive element of the rat .alpha.2-macroglobulin gene (CTGGGA; M. Hattori, L. J. Abraham, W. Northemann, and G. H. Fey,
Proc. Natl. Acad. Sci. USA 87:2364-2368, 1990) are contained within this fragment in immediate juxtaposition and partially overlapping.
Site-directed mutagenesis within this homology region drastically reduced the inducibility of the C3 promoter by either cytokine. DNase I footprinting analysis defined a binding site for the transcription factor CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%/EBP), which included
the IL-1-responsive element-like sequence. No differences were seen between the footprints generated by using extracts from unstimulated and IL-1-stimulated Hep3B2 cells. However, gel retardation analysis revealed two IL-1-specific bands. The data suggest that the induction by IL-1 is mediated by a factor belonging to the family of C/EBP-related proteins.

%%%1990%%%

19/3,AB/44 (Item 44 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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07420800 BIOSIS NO.: 000091026789
IL-6DBP A NUCLEAR PROTEIN INVOLVED IN INTERLEUKIN-6 SIGNAL TRANSDUCTION
DEFINES A NEW FAMILY OF LEUCINE ZIPPER PROTEINS RELATED TO C-EBP
AUTHOR: POLI V; MANCINI F P; CORTESE R
AUTHOR ADDRESS: DEP. GENETICS DEV., COLL. PHYSICIANS SURGEONS, COLUMBIA
UNIV., NEW YORK, N.Y. 10032.
JOURNAL: CELL 63 (3). 1990. 643-653. %%%1990%%%
FULL JOURNAL NAME: Cell
CODEN: CELLB
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: We analyzed a family of proteins from hepatoma cell nuclei that
bind to interleukin-6 responsive elements (IL-6REs) of several acute-phase genes. This family is characterized by leucine zipper domains compatible with that of the CCAAT/enhancer %%%binding%%% %%%protein%%% (
%%%C%%%/EBP). A cDNA clone coding for a member of the family, IL-6DBP,
was isolated; it is strongly homologous to C/EBP in the region of the basic domain and in the leucin zipper sequence. IL-6DBP and C/EBP can interact in vitro to form heterodimers that bind to DNA with the same specificity as the respective homodimers, and they can interact functionally in vivo. Both the DNA binding activity and the trans-activating capacity of IL-6DBP are induced in hepatoma cells by %%%treatment%%% with IL-6 through a posttranslational mechanism, implicating it as a nuclear target of IL-6 and as a mediator of the IL-6-dependent transcriptional activation of liver genes during the acute-phase response.

%%%1990%%%

19/3,AB/45 (Item 45 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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07255794 BIOSIS NO.: 000090035670
INHIBITION OF COFACTOR ACTIVITY OF PROTEIN S BY A COMPLEX OF PROTEIN S AND
C4B-BINDING PROTEIN EVIDENCE FOR INACTIVE TERNARY COMPLEX FORMATION
BETWEEN PROTEIN S C4B-BINDING PROTEIN AND ACTIVATED PROTEIN C
AUTHOR: NISHIOKA J; SUZUKI K
AUTHOR ADDRESS: DIV. ENZYME CYTOL., INST. ENZYME RES., UNIVERSITY
TOKUSHIMA, KURAMOTO-CHO 3, TOKUSHIMA 770, JPN.
JOURNAL: J BIOL CHEM 265 (16). 1990. 9072-9076. %%%1990%%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: To eludicate the mechanism by which C4b-binding protein inhibits
the cofactor activity of protein S for anticoagulant-activated protein C, the interactions between protein S, activated %%%protein%%% %%%C%%%, and
C4b-%%%binding%%% protein were studied using solid-phase enzyme immunoassays. Both activated %%%protein%%% %%%C%%% and C4b-%%%binding%%%
protein bound to protein S fixed to microplate wells. C4b-binding protein did not inhibit the %%%binding%%% of activated %%%protein%%% %%%C%%% to
protein S, nor did activated %%%protein%%% %%%C%%% inhibit the %%%binding%%% of C4b-binding protein to protein S. Activated %%%protein%%% %%%C%%% %%%bound%%% to a protein S-C4b-binding protein
complex which was cross-linked with a chemical reagent as well as it bound to free protein S. Protein S-C4b-binding protein complex competitively inhibited activated %%%protein%%% %%%C%%%-%%%binding%%% to
free protein S and also the cofactor activity of free protein S. Immunoblotting analysis showed ternary complex formation which protein S,
C4b-binding protein, and activated protein C in the liquid phase by

%%%treatment%%% with the cross-linking reagent. These finding suggest that the protein S-C4b-binding protein complex inhibits the cofactor activity of free protein S probably by inhibition of functionally active protein S-activated protein Complex formation by the apparent competitive formation of an inactive ternary complex with protein S, C4b-binding protein, and activated protein C.

%%%1990%%%

19/3,AB/46 (Item 46 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06660930 BIOSIS NO.: 000087103107
AVIAN RETROVIRAL LONG TERMINAL REPEATS BIND CCAAT-ENHANCER-BINDING PROTEIN
AUTHOR: RYDEN T A; BEEMON K
AUTHOR ADDRESS: DEP. BIOL., JOHNS HOPKINS UNIV., BALTIMORE, MD. 21218.
JOURNAL: MOL CELL BIOL 9 (3). 1989. 1155-1164. %%%1989%%%
FULL JOURNAL NAME: Molecular and Cellular Biology
CODEN: MCEBD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: DNA-protein interactions involving enhancer and promoter sequences within the U3 regions of several avian retroviral long terminal repeats (LTRs) were studied by DNase I footprinting. The rat CCAAT/enhancer-%%%binding%%% %%%protein%%%, %%%C%%%/EBP, %%%bound%%% to all four viral LTRs examined. The Rous sarcoma virus binding site corresponded closely to the 5' limit of the LTR enhancer; nucleotides -225 to -188 were protected as a pair of adjacent binding domains. The Fujinami sarcoma virus LTR bound C/EBP at a single site at nucleotides -213 to -195. C/EBP also bound to the promoter region of the enhancerless Rous-associated virus-0 LTR at nucleotides -77 to -57. The avian myeloblastosis virus LTR bound C/EBP at three sites; nucleotides -262 to -246, -154 to -134, and -55 to -39. We have previously observed binding of C/EBP to an enhancer in the gag gene of avian retroviruses. A heat-%%%treated%%% nuclear extract from chicken liver bound to all of the same retroviral sequences as did C/EBP. Alignment of the avian retroviral binding sequences with the published binding sites for C/EBP in two CCAAT boxes and in the simian virus 40, polyoma, and murine sarcoma virus enhancers suggested TGTNNGTCAAGT as a consensus sequence for binding of C/EBP. When two bases of this consensus sequence were altered by site-specific mutagenesis of the Rous sarcoma virus LTR, binding of the heat-stable chicken protein was eliminated.

%%%1989%%%

19/3,AB/47 (Item 47 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

06177645 BIOSIS NO.: 000086011827
A CONSERVED EPITOPE ON SEVERAL HUMAN VITAMIN K-DEPENDENT PROTEINS LOCATION OF THE ANTIGENIC SITE AND INFLUENCE OF METAL IONS ON ANTIBODY BINDING
AUTHOR: CHURCH W R; MESSIER T; HOWARD P R; AMIRAL J; MEYER D; MANN K G
AUTHOR ADDRESS: DEP. BIOCHEM., UNIV. VT., HEALTH SCI. COMPLEX, GIVEN BUILD., BURLINGTON, VT. 05405.
JOURNAL: J BIOL CHEM 263 (13). 1988. 6259-6267. %%%1988%%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: A murine monoclonal antibody (designated H-11) produced by injecting mice with purified human protein C was found to bind several human vitamin K-dependent proteins. Using a solid-phase competitive radioimmunoassay with antibody immobilized onto microtiter plates, binding of 125I-labeled protein C to the antibody was inhibited by increasing amounts of protein C, prothrombin, and Factors X and VII over a concentration range of 1 .times. 10-8 to 1 .times. 10-6 M. Other vitamin K-dependent proteins including Factor IX and protein S did not inhibit or inhibited only at the highest concentration %%%binding%%% of radiolabeled %%%protein%%% %%%C%%% to the immobilized antibody. Chemical %%%treatment%%% of prothrombin with a variety of agents including denaturation by sodium dodecyl sulfate, reduction with mercaptoethanol followed by carboxymethylation with iodoacetic acid, citraconylation of lysine residues, removal of metal ion with EDTA, or heat decarboxylation did not destroy the antigenic site recognized by the antibody as measured by immunoblotting of prothrombin or prothrombin derivative immobilized onto nitrocellulose. Immunoblotting of purified vitamin K-dependent polypeptides with the monoclonal antibody following sodium dodecyl sulfate-polyacrylamide gel electrophoresis and electrophoretic transfer to nitrocellulose indicated that the antigenic site was found on the light chains of protein C and Factor X. Chymotrypsin digestion of prothrombin and isolation on QAE-Sephadex of the peptide representing amino-terminal residues 1-44 of prothrombin further localized the antigenic site recognized by the monoclonal antibody to the highly conserved .gamma.-carboxyglutamic acid-containing domain. The exact location of the antigenic determinant for antibody H-11 was established using synthetic peptides. Antibody H-11 bound specifically to synthetic peptides corresponding to residues 1-12 of Factor VII and 1-22 of protein C. Comparison of protein sequences of bovine and human vitamin K-dependent proteins suggests that the sequence Phe-Leu-Glu-Glu-Xaa-Arg/Lys is required for antibody binding. The glutamic acid residues in this peptide segment are the first 2 .gamma.-carboxyglutamic acid residues near the amino-terminal end in the native proteins. Increasing concentrations of Ca2+, Mg2+, or Mn2+ partially inhibited %%%binding%%% of 125I-%%%protein%%% %%%C%%% to the antibody in a solid-phase assay system with half-maximal binding observed at divalent metal ion concentrations of 2, 4, and 0.6 mM, respectively. The antigenic site thus recognized by monoclonal antibody H-11 is located at the amino-terminal region in the highly conserved .gamma.-carboxyglutamic acid-containing domains of several, but not all, vitamin K-dependent proteins. Furthermore, the binding of metal ions to the protein causes loss of the determinant recognized by the antibody due possibly to a metal ion-dependent conformational change of the amino acid residues located at the amino terminus.

%%%1988%%%

19/3,AB/48 (Item 48 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05756719 BIOSIS NO.: 000084105126
THROMBOMODULIN A COFACTOR OF PROTEIN C ACTIVATION ISOLATION CHARACTERIZATION AND APPLICATION FOR LABORATORY MEDICINE
AUTHOR: KUSUMOTO H
AUTHOR ADDRESS: DEP. LAB. MED., MIE UNIV. SCH. MED., TSU, MIE 514, JPN.
JOURNAL: MIE MED J 37 (1). 1987. 145-172. %%%1987%%%
FULL JOURNAL NAME: Mie Medical Journal
CODEN: MMJJA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: The present study was undertaken to isolate and characterize thrombomodulin, a cofactor in thrombin-catalyzed activation of protein C, from bovine and human lungs. Thrombomodulin was also applied to a functional assay for protein C in plasma. Thrombodulin isolated by diisopropylphosphate-thrombin-agarose column chromatography was a single polypeptide chain with apparent molecular weights of 78,000 and 105,000 before and after reduction, respectively, on sodium dodecyl sulfate (SDS)-polyacrylamide gel electrophoresis. The overall amino acid compositions of bovine and human thrombomodulin were similar to that of the rabbit protein which had been isolated previously (13). The NH2-terminal sequence of human thrombomodulin had a high homology of 64%

with the bovine protein. Thrombomodulin from both species was unusually stable in 1% SDS and 8 M urea, at pH's 2 and 10, and with heat %%%treatment%%% at 60.degree. C, but was unstable against 2-mercaptoethanol %%%treatment%%%. Expression of thrombomodulin cofactor
activity was Ca2+-dependent. Formation of an equimolar complex of thrombin and thrombomodulin was required for maximal protein C activation. Bovine thrombomodulin strongly blocked thrombin-induced fibrinogen clotting and platelet activation as did the rabbit protein, but the inhibitory activity of the human protein was very weak. Thrombomodulin had no influence on the inhibition of thrombin by antithrombin III with or without heparin, protein C inhibitor or synthetic thrombin inhibitors. The functional assay for plasma protein C using thrombomodulin was developed to enable detection of dysfunctional protein C molecules. The assay consisted of three steps; (a) extraction of protein C from plasma by barium citrate precipitation, followed by monoclonal anti-protein C antibody adsorption; (b) activation of %%%protein%%% %%%C%%% %%%bound%%% to the antibody by thrombin-thrombomodulin; (c) measurement of activated protein C using a synthetic chromogenic substrate, S-2366. This assay proved effective in distinguishing normal from abnormal protein C.
%%%1987%%%

19/3,AB/49 (Item 49 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05238970 BIOSIS NO.: 000082079592
THE %%%BINDING%%% OF ACTIVATED %%%PROTEIN%%% %%%C%%% TO FACTORS V AND VA
AUTHOR: KRISHNASWAMY S; WILLIAMS E B; MANN K G
AUTHOR ADDRESS: DEP. BIOCHEM., UNIV. VERMONT, BURLINGTON, VERMONT 05405.
JOURNAL: J BIOL CHEM 261 (21). 1986. 9684-9693. %%%1986%%%
FULL JOURNAL NAME: Journal of Biological Chemistry
CODEN: JBCHA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Activated protein C has been derivatized with the active site-directed fluorophore
2-(dimethylamino)-6-naphthalenesulfonylglutamylglycylarginyl chloromethyl ketone (2,6-DEGR-APC). Covalently modified activated proteint has been used to investigate the binding interactions of the protein to factors V and VaA in the presence of phospholipid vesicles. The fluorescence polarization of the 6-dimethylaminonaphthalene-2-sulfonyl moiety increased saturably with increasing phospholipid concentrations in the presence or absence of factor V or Va. Differences in the limiting polarization values indicated distinguishable differences in the interactions between 2,6-DEGR-APC and phospholipid in the presence of factor V or Va. The dissociation constant calculated for the 2,6-DEGR-APC/phospholipid interaction (7.3 .times. 10-8 M) was not significantly altered by factor V but was decreased to 7 .times. 10-9 M in the presence of factor Va. The interaction between 2,6-DEGR-APC and factor V or Va was characterized by a 1:1 stoichiometry. The binding of 2,6-DEGR-APC to factor V or Va in the presence of phospholipid could be reduced in a competitive manner by diisopropylphosphofluoridate-%%%treated%%% activated protein C. An analysis of the displacement curves
indicated that the binding of 2,6-DEGR-APC was indistinguishable from the binding of diisopropylphosphofluoridate-%%%treated%%% activated protein
C. The interaction between 2,6-DEGR-APC and phospholipid-bound factor VA
was further examined using the isolated subunits of factor Va. Fluorescence polarization changes observed with component E of Va (light chain) closely corresponded with the changes observed with factor Va, whereas isolated component D (heavy chain) had little influence on the binding of 2,6-DEGR-APC to phospholipid vesicles. The data presented are consistent with the interpretation that component E of factor Va contains a binding site for activated protein C.

%%%1986%%%

19/3,AB/50 (Item 50 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

05179729 BIOSIS NO.: 000082020350
SIMPLE IMMUNOCHROMOMETRIC ASSAY FOR PROTEIN C ACTIVITY
AUTHOR: EXNER T; KOUTTS J
AUTHOR ADDRESS: HAEMATOL. DEP., WESTMEAD HOSP., WESTMEAD, SYDNEY, AUST.
2145.
JOURNAL: J LAB CLIN MED 107 (5). 1986. 405-411. %%%1986%%%
FULL JOURNAL NAME: Journal of Laboratory and Clinical Medicine
CODEN: JLCMA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: %%%Protein%%% %%%C%%% %%%binds%%% readily from human plasma to
antibody-coated wells, where it may be quantitated with an iodine 125-labeled antibody to protein C. %%%Treatment%%% with thrombin results
in a small reduction in the protein C antigen detectable by this immunoradiometric assay (IRMA). However, activated protein C resulting from thrombin %%%treatment%%% and retained by the antibody on a solid phase may be detected by an overnight incubation with chromogenic substrates S-2366 or CBS 34.47. The immunochromometric assay (ICMA, analogous to IRMA) described uses of heterologous antibody to protein C, activation with relatively low concentrations of bovine thrombin, and quantitation by hydrolysis of chromogenic substrate in a convenient 96-well microtiter plate system. The correlation between IRMA and ICMA protein C results was found to be good with normal persons and patients with liver disease. Patients taking oral anticoagulants had reduced protein C antigen (IRMA) but even lower protein C by ICMA, indicating that inactive forms were present.

%%%1986%%%

19/3,AB/51 (Item 51 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)

04761732 BIOSIS NO.: 000080064859
DETERMINATION OF PLASMA PROTEIN S THE PROTEIN COFACTOR OF ACTIVATED PROTEIN
C
AUTHOR: BERTINA R M; VAN WIJNGAARDEN A; REINALDA-POOT J; POORT S R; BOM V J
J
AUTHOR ADDRESS: HAEMOSTASIS THROMBOSIS RES. UNIT, DEP. HAEMATOL., LEIDEN
UNIV. HOSP., RIJNSBURGERWEG 10, 2333 AA LEIDEN, NETHERLANDS.
JOURNAL: THROMB HAEMOSTASIS 53 (2). 1985. 268-272. %%%1985%%%
FULL JOURNAL NAME: Thrombosis and Haemostasis
CODEN: THHAD
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Protein S, an important cofactor of activated %%%protein%%%
%%%C%%%, and C4b-%%%binding%%% protein were purified from human plasma.
Specific antibodies against the purified proteins were raised in rabbits and used for the development of immunologic assays for these proteins in plasma: an immunoradiometric assay for protein S (which measures both free protein S and protein S complexed with C4b-binding protein) and an electroimmunoassay for C4b-binding protein. Ranges for the concentrations of these proteins were established in healthy volunteers and patients using oral anticoagulant therapy. A slight decrease in protein S antigen was observed in patients with liver disease (0.78 .+-. 0.25 U/ml); no significant decrease in protein S was observed in patients with DIC [dissimenated intravascular coagulation] (0.95 .+-. 0.25 U/ml). Criteria were developed for the laboratory %%%diagnosis%%% of an isolated protein
S deficiency.

%%%1985%%%

19/3,AB/52 (Item 52 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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04651784 BIOSIS NO.: 000079064821
QUANTITATION OF HUMAN PROTEIN S IN THE PLASMA OF NORMAL AND WARFARIN-
%%%TREATED%%% INDIVIDUALS BY RADIOIMMUNOASSAY
AUTHOR: FAIR D S; REVAK D J
AUTHOR ADDRESS: DEP. IMMUNOL., RES. INST. SCRIPPS CLINIC, 10666 N. TORREY
PINES ROAD, LA JOLLA, CALIF., USA.
JOURNAL: THROMB RES 36 (6). 1984 (RECD. 1985). 527-536.
%%%1984%%%
FULL JOURNAL NAME: Thrombosis Research
CODEN: THBRA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Protein S was purified from human plasma and used to raise monospecific antibodies. A double antibody equilibrium radioimmunoassay was constructed and met all the requirements for a sensitive, accurate and specific determination of protein S. The sensitivity of the assay was between 8 and 250 ng of protein S/ml and the coefficient of variation was 2-6% within assays and 13-19% between assays. Complement C4b-%%%binding%%% protein or %%%protein%%% %%%C%%% did not effect the measurement of protein S. Complete competition with parallel slopes of inhibition was seen among purified protein S and plasma from normal and warfarin-%%%treated%%% individuals indicating immunochemical identity and validating the measurement of protine S in plasma. The concentration of protein S in normal plasma (n = 24) was 23.4 .+-. 4.42 .mu.g/ml and in plasma from warfarin-%%%treated%%% individuals (n = 24) was 12.6 .+-. 3.92 .mu.g/ml. A common feature of individuals undergoing warfarin therapy is the reduction of .apprx. 50% in the concentration of each of the vitamin K-dependent proteins.

%%%1984%%%

19/3,AB/53 (Item 53 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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04209345 BIOSIS NO.: 000077035389
CIRCULATING IMMUNE COMPLEXES AND COMPLEMENT C-1 ACTIVATION IN PATIENTS WITH
RAPIDLY PROGRESSIVE GLOMERULO NEPHRITIS BEFORE AND AFTER %%%TREATMENT%%%
WITH IMMUNO SUPPRESSION AND PLASMA EXCHANGE
AUTHOR: SJOHOLM A G; BRUN C; LARSEN S; THYSELL H
AUTHOR ADDRESS: DEP. NEPHROL., UNIV. HOSP., S-221 85 LUND.
JOURNAL: INT ARCH ALLERGY APPL IMMUNOL 72 (1). 1983. 9-15.
%%%1983%%%
FULL JOURNAL NAME: International Archives of Allergy and Applied Immunology
CODEN: IAAAA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Well-known assays (C1q binding assay, C1q deviation test, solid-phase C1q binding assay, solid-phase conglutinin binding assay, and the platelet aggregation test) for detection of circulating immune complexes (CIC) were used in 30 patients with different kinds of rapidly progressive glomerulonephritis. In 89% of the patients evidence of CIC was found in at least one of the assays; 81% of the patients were positive in the C1q binding assay and/or the conglutinin binding assay with addition of complement. CIC were more often detected by several assays, and with higher values in patients with systemic disease than in patients with renal involvement alone. CIC were found in 2 patients with Goodpasture's syndrome. Fifteen patients were reexamined after %%%treatment%%% with plasma exchange, when the disease was clinically inactive. The patients were still on immunosuppressive %%%treatment%%%. In most of these, CIC were detectable, but with lower values than at the start of %%%treatment%%%. Before %%%treatment%%%, high levels of C.hivin.1r-C.hivin.1s-C.hivin.1 inactivator complexes suggested increased C1 activation in 93% of the patients. C-reactive protein was raised, and the concentrations of C1q, C1s, C4, C3 and factor B were normal or high in most of the patients. Pronounced hypocomplementemia was found only in 2 patients with systemic lupus erythematosus (SLE). After %%%treatment%%% , the levels of C-reactive protein, C1q, C1s, C3 and factor B had decreased in the non-SLE patients, while the average levels of C4 and C.hivin.1r-C.hivin.1s-C.hivin.1 inactivator complexes were essentially unchanged.

%%%1983%%%

19/3,AB/54 (Item 54 from file: 5)
DIALOG(R)File 5:Biosis Previews(R)
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02947407 BIOSIS NO.: 000069055525
THE INHIBITION OF BLOOD COAGULATION BY ACTIVATED PROTEIN C THROUGH THE
SELECTIVE INACTIVATION OF ACTIVATED FACTOR-V
AUTHOR: WALKER F J; SEXTON P W; ESMON C T
AUTHOR ADDRESS: SECT. EXP. PATHOL. MED., UNIV. OKLA. HEALTH SCI. CENT.,
OKLAHOMA CITY, OKLA. 73190, USA.
JOURNAL: BIOCHIM BIOPHYS ACTA 571 (2). 1979 (RECD. 1980). 333-342.
%%%1979%%%
FULL JOURNAL NAME: Biochimica et Biophysica Acta
CODEN: BBACA
RECORD TYPE: Abstract
LANGUAGE: ENGLISH

ABSTRACT: Activated protein C inhibited factor [F] Xa initiated clotting of [bovine] plasma. Activated protein C did not inhibit prothrombin activation by FXa and Ca2+ or FXa, Ca2+ and lipid. Activated protein C did inhibited prothrombin activation by FXa, Ca2+ and FVa or FXa, Ca2+, lipid and FVa. Excess FVa could reverse the inhibition of prothrombin activation. Incubation of FV with activated protein C had little effect of FV activity in the presence or absence of phospholipid. Preincubation of FV with activated protein C had no effect upon the degree to which FV could be activated. When FV was activated with thrombin in the presence of activated protein C, rapid decline in FVa activity was observed. When activated protein C was incubated with purified FVa in the absence of thrombin, a similar rapid decay in FVa activity was observed. Activated protein C-catalyzed decay of FVa activity was not obligatorily dependent on the presence of lipid. Lipid enhanced the rate of inactivation. Analysis of sodium dodecyl sulfate gels of FV or Va %%%treated%%% with activated protein C indicated that activated protein C degraded a slow migrating band of the FV doublet and that it also was able to degrade both the heavy and light chains of FVa. Activated Protein C could apparently inhibit FXa initiated clotting by degrading FVa. FVa could be protected from activated protein C inactivation by the presence of FXa, suggesting that activated %%%protein%%% %%%C%%% %%%binds%%% to FVa at or near the FXa binding site. Specificity of activated protein C for FVa and ability of FXa to stabilize FVa may play important functions in the regulation of blood coagulation.

%%%1979%%%

19/3,AB/55 (Item 1 from file: 73)
DIALOG(R)File 73:EMBASE
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07034725 EMBASE No: 1997315138
Signaling pathways through which insulin regulates CCAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBPalpha) phosphorylation and gene
expression in 3T3-L1 adipocytes. Correlation with GLUT4 gene expression
Hemati N.; Ross S.E.; Erickson R.L.; Groblewski G.E.; MacDougald O.A.
O.A. MacDougald, Dept. of Physiology, Univ. of Michigan Medical School, 1301 E. Catherine Rd., Ann Arbor, MI 48109-0622 United States
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Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1997 , 272/41 (25913-25919)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 51

%%%Treatment%%% of 3T3-L1 adipocytes with insulin (IC$D5inf 0 ~200 pM
insulin) or insulin-like growth factor-1 (IC$D5inf 0 ~200 pM IGF-1)
stimulates dephosphorylation of CCAAT/enhancer binding protein alpha
(C/EBPalpha), a transcription factor involved in preadipocyte
differentiation. As assessed by immunoblot analysis of one- and
two-dimensional PAGE, insulin appears to dephosphorylate one site within
p30C/EBPalpha and an additional site within p42C/EBPalpha. Consistent
with
insulin causing dephosphorylation of C/EBPalpha through activation of
phosphatidylinositol 3-kinase, addition of phosphatidylinositol 3-kinase
inhibitors (e.g. wortmannin) blocks insulin- stimulated dephosphorylation
of C/EBPalpha. In the absence of insulin, wortmannin or LY294002 enhance
C/EBPalpha phosphorylation. Similarly, blocking the activity of
FKBP-rapamycin-associated protein with rapamycin increases
phosphorylation
of C/EBPalpha in the absence of insulin. Dephosphorylation of C/EBPalpha
by
insulin is partially blocked by rapamycin, consistent with a model in which
activation of FKBP-rapamycin-associated protein by phosphatidylinositol
3-kinase results in dephosphorylation of C/EBPalpha. The dephosphorylation
of C/EBPalpha by insulin, in conjunction with the insulin- dependent
decline in C/EBPalpha mRNA and protein, has been hypothesized to play a
role in repression of GLUT4 transcription by insulin. Consistent with this
hypothesis, the decline of GLUT4 mRNA following exposure of adipocytes
to
insulin correlates with dephosphorylation of C/EBPalpha. However, the
repression of C/EBPalpha mRNA and protein levels by insulin is blocked
with
an inhibitor of the mitogen-activated protein kinase pathway without
blocking the repression of GLUT4 mRNA, thus dissociating the regulation of
C/EBPalpha and GLUT4 mRNAs by insulin. A decline in C/EBPalpha
mRNA and
protein may not be required to suppress GLUT4 transcription because insulin
also induces expression of the dominant-negative form of C/EBPbeta (liver
inhibitory protein), which blocks transactivation by C/EBP transcription
factors.

19/3,AB/56 (Item 2 from file: 73)
DIALOG(R)File 73:EMBASE
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06987235 EMBASE No: 1997273316
Serum mannan-binding lectin (MBL) in patients with infection: Clinical and laboratory correlates
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APMIS (APMIS) (Denmark) 1997, 105/8 (617-622)
CODEN: APMSE ISSN: 0903-4641
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH
NUMBER OF REFERENCES: 17

In this study, we determined the serum levels of mannan-binding lectin (MBL) in patients with suspected or documented infection to characterize the possible role of MBL in the susceptibility to infection. We also investigated the kinetics of MBL during the infection and correlated the concentrations of MBL with those of acute-phase reactants C-reactive protein (CRP) and group II phospholipase A2 (PLAinf 2-II) and cytokines interleukin-1(IL-1), interleukin-6 (IL-6) and tumor necrosis factor alpha (TNF-alpha). The frequency of MBL deficiency in the patients with signs of infection did not differ from that of controls. In four patients with MBL deficiency, the infections were caused by common pathogens and the outcome
was normal. The mean MBL concentration in the patients with signs of infection was significantly higher than in the healthy controls (9.88 and 4.48 mg/l, respectively; $p<0.05$). The highest mean MBL concentration was observed in patients with clinically or microbiologically documented bacterial infection. During follow-up, the MBL concentration altered individually in different patients, but no particular change in pattern in the MBL concentration could be demonstrated in any patient group. Of the acute-phase reactants in the circulation, only CRP and IL-1 showed a weak, albeit significant, negative correlation with the concentration of MBL. In conclusion, the deficiency of MBL was not shown to be an independent risk factor for infection in the adult population studied. The concentration of MBL did not follow the change in pattern of other acute- phase reactants and cytokines during the acute phase response. Therefore, measurement of the MBL concentration as an acute-phase reactant is not useful in the %%%diagnosis%%% or follow-up of infection. On the other hand, the deficiency of MBL can be detected reliably by serological methods even during an infection.

19/3,AB/57 (Item 3 from file: 73)
DIALOG(R)File 73:EMBASE
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06689867 EMBASE No: 1996354799
Calciphylaxis (1)
Walsh J.S.; Fairley J.A.; Hafner J.
Department of Dermatology, Medical College of Wisconsin, 8701 Watertown
Plank Rd.,Milwaukee, WI 53226 United States
Journal of the American Academy of Dermatology (J. AM. ACAD. DERMATOL.)
(United States) 1996, 35/5 I (786-787)
CODEN: JAADD ISSN: 0190-9622
DOCUMENT TYPE: Journal; Letter
LANGUAGE: ENGLISH

19/3,AB/58 (Item 4 from file: 73)
DIALOG(R)File 73:EMBASE
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06612031 EMBASE No: 1996276804
cAMP activation of phosphoenolpyruvate carboxykinase transcription in renal LLC-PKinf 1-Fsup + cells
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Dept. of Biochemistry/Molec. Biology, Colorado State University,Fort Collins, CO 80523-1870 United States
American Journal of Physiology - Renal Fluid and Electrolyte Physiology (AM. J. PHYSIOL. RENAL FLUID ELECTROLYTE PHYSIOL.) (United States) 1996
, 271/2 40-2 (F347-F355)
CODEN: AJPFD ISSN: 0363-6127
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Phosphoenolpyruvate carboxykinase (PCK) is a key regulatory enzyme in renal ammoniagenesis and gluconeogenesis. LLC-PKinf 1-Fsup + cells are porcine renal proximal tubule-like cells that express significant levels of the cytosolic PCK. %%%Treatment%%% of subconfluent LLC-PKinf 1-Fsup + cells
with 0.1 mM 8- (4-chlorophenylthio)-adenosine 3',5'-cyclic monophosphate (CPT-cAMP) for 8 h causes a 21-fold increase in PCK mRNA. This response is
very rapid and is not inhibited by 0.5 mM cycloheximide, indicating that ongoing protein synthesis is not required. Similarly, cells transfected with PCK inf 4inf 9inf 0CAT exhibit an 8- to 10-fold increase in chloramphenicol acetyltransferase (CAT) activity when %%%treated%%% with
cAMP for 24 h. The addition of okadaic acid, a protein phosphatase inhibitor, both stimulated the CAT activity and potentiated the cAMP effect by twofold, suggesting that phosphorylation may contribute to the transcriptional activation. Assays using a series of PCK-CAT constructs containing specific deletions or block mutations established that the CRE-1 the P3(II) elements are required for the cAMP response. Cotransfection experiments using dominant negative expression vectors indicated that a CCAAT enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) transcription
factor, and not CREB, mediates cAMP activation of transcription in LLC-PKinf 1-Fsup + cells.

19/3,AB/59 (Item 5 from file: 73)
DIALOG(R)File 73:EMBASE

06560091 EMBASE No: 1996221019
GADD153/CHOP, a DNA damage-inducible protein, reduced CAAT/enhancer
binding protein activities and increased apoptosis in 32d cl3 myeloid cells
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United States
Cancer Research (CANCER RES.) (United States) 1996, 56/14 (3250-3256)
CODEN: CNREA ISSN: 0008-5472
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

GADD153/CHOP is a DNA damage-inducible, nuclear leucine zipper protein
that is capable of producing a Ginf 1-S arrest in fibroblastic cells and of dimerizing with and inhibiting CAAT/enhancer %%%binding%%% %%%protein%%% (%%%C%%%/EBP) activities. CHOP was induced in 32D cl3 myeloid cells exposed
to methylmethane sulfonate (MMS), a DNA alkylating agent. The degree of induction was dependent upon the dose of MMS to which the cells were exposed. CHOP was not expressed, at least at similar levels, during 32D cl3 cell granulocytic differentiation or during their apoptosis upon growth factor withdrawal. High-level expression of exogenous CHOP in 32D cl3 cells
markedly inhibited the trans-activation activities of endogenous C/EBPs. These cells proliferated in IL-3, although low-level ongoing apoptosis not observed with control cells was detected. When these cultures were transferred to granulocyte colony-stimulating factor (G-CSF), the majority of the cells underwent apoptosis, although the levels of CHOP did not increase. Similarly, 32D cl3 cells %%%treated%%% with doses of MMS sufficient to induce endogenous CHOP underwent apoptosis more rapidly when
placed in G-CSF-containing, compared with interleukin 3 (IL-3)containing, medium. However, induction of CHOP by MMS was similar in IL-3 and in G-CSF.
The heightened sensitivity of 32D cl3 cells to CHOP in G-CSF could result either from the loss of IL-3-specific signals or from increased expression of C/EBPs. Because myeloid leukemias express C/EBPalpha, induction of CHOP
might contribute to their chemotherapy- induced apoptosis, and alterations in CHOP expression could contribute to their development of chemotherapy resistance.

19/3,AB/60 (Item 6 from file: 73)
DIALOG(R)File 73:EMBASE

06455576 EMBASE No: 1996118153
CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%/EBPalpha) inhibits
cell proliferation through the p21 (WAF-1/CIP-1/SDI-1) protein
Timchenko N.A.; Wilde M.; Nakanishi M.; Smith J.R.; Darlington G.J.
Department of Pathology, Baylor College of Medicine,Houston, TX 77071 United States
Genes and Development (GENES DEV.) (United States) 1996, 10/7 (804-815)
CODEN: GEDEE ISSN: 0890-9369
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

C/EBPalpha has a role in growth arrest and differentiation of mouse preadipocytes. To study the mechanism of C/EBPalpha-induced growth arrest,
we developed a cell line, HT1, that contained the human C/EBPalpha gene under Lac repressor control. IPTG-induced C/EBPalpha caused inhibition of cell proliferation and DNA synthesis as measured by colony growth assays, cell counting, and BrdU uptake. A number of proteins that are known to be involved in the regulation of the cell cycle, such as cyclin-dependent kinase (CDK) 2 and CDK4, proliferating cell nuclear antigen (PCNA), p53, c-fos, and the CDK inhibitor p16 and p27 were investigated by Western analysis. No change in their expression was observed. However, the p21 (WAF-1/CIP-1/SDI-1) protein was significantly elevated in growth-arrested HT1 cells. Elevation of p21/SDI-1 mRNA (threefold) and activation of the p21/SDI-1 promoter by C/EBPalpha did not account for the 12- to 20-fold increase in p21/SDI-1 protein. Protein synthesis inhibition by cycloheximide (CHX) %%%treatment%%% indicated that the half-life of p21/SDI-1 in dividing HT1 cells was ~30 min. However, in C/EBPalpha growth-arrested cells, the level of the p21/SDI-1 did not change for >80 min after CHX addition. Our studies demonstrate that C/EBPalpha activates p21/SDI-1 by increasing p21/SDI-1 gene expression and by post-translational stabilization of p21/SDI-1 protein. Furthermore, induction of p21/SDI-1 is responsible for the ability of C/EBPalpha to inhibit proliferation because transcription of antisense p21/SDI-1 mRNA eliminated growth inhibition by C/EBPalpha.

19/3,AB/61 (Item 7 from file: 73)
DIALOG(R)File 73:EMBASE

06338984 EMBASE No: 1995369032
Effect of phenylephrine and prazosin on the somatostatinergic system in the rat frontoparietal cortex
Lopez-Sanudo S.; Rodriguez-Martin E.; Martin-Espinosa A.; Arilla E.
Unidad de Neuroendocrin. Molecular, Departamento de Bioquimica, Facultad
de Medicina,E-28871, Alcala de Henares, Madrid Spain
Peptides (PEPTIDES) (United States) 1995, 16/8 (1453-1459)
CODEN: PEPTD ISSN: 0196-9781
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Somatostatin (SS) and noradrenaline (NA) are distributed in the rat cerebral cortex, and seizure activity is one of the aspects of behavior affected by both neurotransmitters. Due to the possible interaction between both neurotransmitter systems, we studied whether phenylephrine, an alphainf 1-adrenoceptor agonist, and prazosin, an alphainf 1-adrenoceptor antagonist, can modulate SS-like immunoreactivity (SS-LI) levels, binding of (sup 1sup 2sup 5I)(Tyrsup 1sup 1)SS to its specific receptors, the ability of SS to inhibit adenylate cyclase (AC) activity, and the guanine nucleotide %%%binding%%% regulatory %%%protein%%% %%%C%%%(i) and Cinf 0 in
the Sprague-Dawley rat frontoparietal cortex. An IP dose of 2 or 4 mg/kg of phenylephrine injected 7 h before decapitation decreased the number of SS receptors and increased the apparent affinity in frontoparietal cortex membranes. An IP dose of 20 or 25 mg/kg of prazosin administered 8 h before
decapitation increased the number of SS receptors and decreased their apparent affinity. The administration of prazosin before the phenylephrine injection prevented the phenylephrine-induced changes in SS binding. The addition of phenylephrine and/or prazosin 10sup -sup 5 M to the incubation medium changed neither the number nor the affinity of the SS receptors in the frontoparietal cortex membranes. Phenylephrine or prazosin affected neither SS-LI content nor the basal or forskolin (FK)-stimulated AC activities in the frontoparietal cortex. In addition, SS caused an equal inhibition of AC activity in frontoparictal cortex membranes of phenylephrine- and prazosin-%%%treated%%% rats compared with the respective
control group. Finally, phenylephrine and prazosin did not vary the pertussis toxin (PTX)-catalyzed ADP ribosylation of G(i)- and/or Ginf 0-proteins. These results suggest that the above-mentioned changes are related to the phenylephrine activation of alphainf 1-adrenoceptors or to the blocking of these receptors by prazosin. In addition, these data provide further support for a functional interrelationship between the alphainf 1-adrenergic and somatostatinergic systems in the rat frontoparietal cortex.

19/3,AB/62 (Item 8 from file: 73)
DIALOG(R)File 73:EMBASE

06300656 EMBASE No: 1995330542
Transcriptional regulation of human prostaglandin-endoperoxide synthase-2 gene by lipopolysaccharide and phorbol ester in vascular endothelial cells. Involvement of both nuclear factor for interleukin-6 expression site and cAMP response element
Inoue H.; Yokoyama C.; Hara S.; Tone Y.; Tanabe T.
Department of Pharmacology, NCCRI, 5-7-1 Fujishiro-dai,Suita, Osaka 565 Japan

Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1995 , 270/42 (24965-24971)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

There exist two distinct isozymes of prostaglandin-endoperoxide synthase (PES). PES-2 mRNA is synergistically induced by lipopolysaccharide (LPS) and 12-O-tetradecanoylphorbol-13-acetate (TPA) in bovine arterial endothelial cells. On the other hand, PES-1 mRNA is constitutively expressed under these conditions. Therefore, the promoter activities of the human genes for PES-1 and -2 in bovine arterial endothelial cells were examined. The 5'-flanking region of the human PES-2 gene (nucleotides -327 to +59) showed promoter activity inducible by LPS and TPA using transient transfection analysis, whereas that of the PES-1 gene (nucleotides -1010 to +69) showed constitutive promoter activity. Destruction of both consensus sequences for the nuclear factor responsible for the interleukin-6 expression (NF-IL6) site (nucleotides -132 to -124) and the cyclic AMP response element (CRE) (nucleotides -59 to -53) of the human PES-2 gene markedly reduced the promoter activity (25%) of the PES-2 gene after combined %%%treatment%%% with LPS and TPA, although single destruction of
the NF-IL6 site or the CRE slightly reduced the promoter activity (60 or 90%, respectively). Moreover, cotransfecfion experiments showed that a trans-acting factor, CCAAT enhancer %%%binding%%% %%%protein%%% (%%%C%%% /EBPdelta), which %%%binds%%% to both the NF-IL6 site and the CRE, increased the promoter activity of the PES-2 gene mainly through the CRE. C/EBPdelta mRNA was rapidly induced by LPS. Collectively, these results suggest that transcription of the PES-2 gene in vascular endothelial cells is regulated through combination of the NF-IL6 site and the CRE and that C/EBPdelta functions as one of the trans-acting factors.

19/3,AB/63 (Item 9 from file: 73)
DIALOG(R)File 73:EMBASE
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06175621 EMBASE No: 1995199102
Lupus anticoagulants: Clinic, pathophysiology, %%%diagnosis%%% and therapy
LUPUS-ANTIKOAGULANS: KLINIK, PATHOPHYSIOLOGIE, %%%DIAGNOSTIK%%% UND THERAPIE
Potzsch B.; Madlener K.
Kerckhoff-Klinik, Abteilung Hamostaseologie, Transfusionsmedizin, Sprudelhof 11,D-61231 Bad Nauheim Germany
Hamostaseologie (HAMOSTASEOLOGIE) (Germany) 1995, 15/2 (100-104)
CODEN: HAEMD ISSN: 0720-9355
DOCUMENT TYPE: Journal; Review
LANGUAGE: GERMAN SUMMARY LANGUAGE: ENGLISH; GERMAN

Lupus anticoagulants (LA) are autoantibodies directed against negatively charged phospholipids. The presence of LA is closely associated with the occurrence of arterial and venous thrombosis, thrombocytopenia, and recurrent abortion. However, the nature of the association between LA and these clinical events is unknown. Competition of LA and activated %%%protein%%% %%%C%%% for %%%binding%%% sites on negatively charged
phospholipids resulting in an acquired APC dysfunction has been reported by several authors and may be one cause of thrombosis in LA. A recommended system for detecting and confirming LA is to use phospholipid depleted tests such as the Kaolin-Clotting-Time, the Textarin-Ecarin-Ratio, or modified a PTTs to initially screen for LA. An anticoagulant should be subsequently confirmed by failure to correct the defect in a mixture of test and normal plasma or by a relative correction of the LA defect by addition of phospholipids. Patients %%%diagnosed%%% as positive for LA and
showing a history of thrombosis should be referred to oral anticoagulation until LA values reach base-line levels.

19/3,AB/64 (Item 10 from file: 73)
DIALOG(R)File 73:EMBASE
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05918666 EMBASE No: 1994331970
Autoantibodies to phospholipid-binding plasma proteins: A new view of lupus anticoagulants and other 'antiphospholipid' autoantibodies
Roubey R.A.S.
Division of Rheumatology/Immunology, Faculty Laboratory Office Building, University of North Carolina,Chapel Hill, NC 27599-7280 United States
Blood (BLOOD) (United States) 1994, 84/9 (2854-2867)
CODEN: BLOOA ISSN: 0006-4971
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH

19/3,AB/65 (Item 11 from file: 73)
DIALOG(R)File 73:EMBASE
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05607921 EMBASE No: 1994012173
Hypercoagulable states
Nachman R.L.; Silverstein R.
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United States
Annals of Internal Medicine (ANN. INTERN. MED.) (United States) 1993, 119/8 (819-827)
CODEN: AIMEA ISSN: 0003-4819
DOCUMENT TYPE: Journal; Review
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Purpose: To describe the major pathophysiologic mechanisms underlying inherited and secondary hypercoagulable states and to evaluate the frequency, natural history, %%%diagnosis%%%, and management of the various
clinical disorders. Data Sources and Study Selection: Relevant clinical literature obtained from bibliographies in hematology textbooks and from computerized indexes was reviewed. A hypothesis was formed based on this literature review and on recent developments from a number of experimental studies. Data Synthesis: Hypercoagulable states include various inherited as well as acquired clinical disorders characterized by an increased risk for thromboembolism. Primary hypercoagulable states include relatively rare inherited conditions that lead to disordered endothelial cell thromboregulation. These conditions include decreased thrombomodulin-dependent activation of activated %%%protein%%% %%%C%%%, impaired heparin %%%binding%%% of antithrombin III, or down-regulation of
membrane- associated plasmin generation. The major, inherited, inhibitor disease states include antithrombin III deficiency, protein C deficiency, and protein S deficiency and should be considered in patients who have recurrent, familial, or juvenile deep-vein thrombosis or occlusion in an unusual location such as a mesenteric, brachial, or cerebral vessel. Secondary hypercoagulable states may be seen in many heterogeneous disorders. In many of these conditions, endothelial activation by cytokines leads to loss of normal vessel-wall anticoagulant surface functions with conversion to a proinflammatory thrombogenic phenotype. Important clinical syndromes associated with substantial thromboembolic events include the antiphospholipid syndrome, heparin-induced thrombopathy, the myeloproliferative syndromes, and cancer. Conclusions: Physiologic thromboregulation occurs at the vessel-wall surface. Quantitative and qualitative deficiencies of normal, steady-state endothelial anticoagulant activities are associated with primary hypercoagulable states. Activated endothelial cell surfaces express a thrombogenic phenotype and contribute to secondary or acquired hypercoagulability.

19/3,AB/66 (Item 12 from file: 73)
DIALOG(R)File 73:EMBASE
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05183761 EMBASE No: 1992323995
Blockade of protein C activation reduces microvascular surgical blood loss
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Department of Surgery, Oklahoma Univ. Health Sciences Ctr.,Oklahoma City,
OK 73104 United States
Journal of Surgical Research (J. SURG. RES.) (United States) 1992, 52/6 (560-564)

CODEN: JSGRA ISSN: 0022-4804
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Protein C is a natural anticoagulant glycoprotein which prevents intravascular clot formation. Protein C functions as an anticoagulant when converted to an active serine protease (activated protein C). Activated protein C is formed at the site of the endothelial injury in response to blood clotting and helps limit the size of blood clots. We tested the hypothesis that by temporarily blocking the activation of intrinsic protein C, we could reduce subsequent surgical blood loss from a microvascular surgical wound. The formation of activated protein C was blocked systemically by intravenous administration of a monoclonal antibody (HPCinf 4) which %%%binds%%% to circulating %%%protein%%% %%%C%%% and prevents its
conversion to activated protein C. Domestic pigs were blindly pretreated with intravenous HPCinf 4 or saline then underwent partial-thickness skin graft harvesting to create a reproducible microvascular wound. Blood loss was measured from each wound and the hemostatic effect of protein C blockade was compared to intravenous saline alone as well as to topical thrombin or thromboplastin. We found that blocking the activation of protein C significantly (P = 0.005) reduces surgical blood loss in this model by 27% compared to saline control animals. Intravenous HPCinf 4 performed equally as well as topical thrombin or tissue thromboplastin. In addition, topical thrombin acted synergistically with HPCinf 4 to reduce blood loss an additional 44% (P = 0.01) as compared to intravenous HPCinf 4 or topical thromboplastin alone. Autopsies perfonned 1 week after HPCinf 4 %%%treatment%%% showed no evidence of systemic thrombosis resulting from
the protein C blockade. This study reveals that blocking the formation of the natural anticoagulant, activated protein C prior to surgery provides a systemic means of reducing capillary bleeding from vascular beds.

19/3,AB/67 (Item 13 from file: 73)
DIALOG(R)File 73:EMBASE
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05175813 EMBASE No: 1992316047
Calcium ionophore A23187 induces expression of the growth arrest and DNA
damage inducible CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%
/EBP)-related gene, gadd153. Casup 2sup + increases transcriptional activity and mRNA stability
Bartlett J.D.; Luethy J.D.; Carlson S.G.; Sollott S.J.; Holbrook N.J.
Laboratory of Molecular Genetics, National Institute on Aging,Baltimore, MD 21224 United States
Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1992 , 267/28 (20465-20470)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

gadd153 is a CCAAT/enhancer-%%%binding%%% %%%protein%%% (%%%C%%%
/EBP)-related gene whose expression is induced in response to growth arrest and DNA damage. This investigation explored the possibility that Casup 2sup + might play a role in regulating expression of gadd153. We have demonstrated that %%%treatment%%% of HeLa cells with the calcium ionophores
A23187 and ionomycin leads to the induction of gadd153 mRNA. The induction
was rapid; increases in mRNA were detected by 90 min of %%%treatment%%%,
and near maximum levels were achieved within 5-h exposure to A23187. Elevated mRNA levels resulted from both an increase in the rate of gadd153 transcription and an increase in the stability of the gadd153 mRNA. The response was not dependent on protein kinase C nor was it coupled to c-fos expression. Buffering intracellular and extracellular Casup 2sup + by combined %%%treatment%%% with BAPTA-AM (acetoxymethyl ester form of
bis(aminophenoxy)ethane N,N'-tetraacetic acid) and EGTA prevented the induction of gadd153 mRNA by A23187. In addition, these %%%treatments%%%
prevented the induction of gadd153 mRNA in response to the DNA damaging agent methyl methanesulfonate. We conclude that intracellular Casup 2sup + plays a role in regulating gadd153 expression. More specifically, Casup 2sup + likely plays a role in the induction of gadd153 mRNA following DNA damage.

19/3,AB/68 (Item 14 from file: 73)
DIALOG(R)File 73:EMBASE
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05165967 EMBASE No: 1992306200
slow border cells, a locus required for a developmentally regulated cell migration during oogenesis, encodes drosophila C/EBP
Montell D.J.; Rorth P.; Spradling A.C.
Department of Biological Chemistry, Johns Hopkins Univ. Sch. of Medicine,Baltimore, MD 21205 United States
Cell (CELL) (United States) 1992, 71/1 (51-62)
CODEN: CELLB ISSN: 0092-8674
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

During Drosophila oogenesis six to ten follicle cells, the border cells, undergo a dramatic and stereotypic migration through the developing egg chamber. We identified four independent P element insertion mutations that specifically blocked border cell migration. They defined a single, novel locus that was named slow border cells (slbo), because hypomorphic alleles caused delayed onset of the migration. Laser ablation of the border cells, or failure of their migration, caused improper morphogenesis of the micropyle, the eggshell structure through which the sperm enters at fertilization. The slbo locus was found to encode a product homologous to the CCAAT/enhancer- %%%binding%%% %%%protein%%% (%%%C%%%/EBP), a basic
region-leucine zipper transcription factor. Drosophila C/EBP may be required for the expression of gene products mediating border cell migration.

19/3,AB/69 (Item 15 from file: 73)
DIALOG(R)File 73:EMBASE
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05113728 EMBASE No: 1992253944
The possible inhibitory role of the leucine-zipper DNA %%%binding%%% %%%protein%%% %%%c%%%- fos in the regulation of hepatic gene expression
after sepsis
Barke R.A.; Brady P.S.; Roy S.; Charboneau R.; Brady L.J.
Department of Surgery, Minneapolis VA Medical Center, 1 Veterans Dr.,Minneapolis, MN 55417 United States
Surgery (SURGERY) (United States) 1992, 112/2 (412-418)
CODEN: SURGA ISSN: 0039-6060
DOCUMENT TYPE: Journal; Conference Paper
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

Background. The leucine-zipper c-fos has been implicated in the regulation of gene expression. We investigated the possible role of c-fos in the regulation of hepatic gene expression after sepsis. Based on previous data demonstrating that sepsis inhibits hepatic gene expression of carnitine palmitoyltransferase (CPT), we hypothesized that c-fos may play a role in the inhibition of CPT gene expression after sepsis. Methods. We studied c-fos gene expression after peritoneal sepsis induced by cecal ligation and puncture (CLP) or sham-CLP. To investigate the possible inhibitory role of c- fos on CPT gene transcription, we investigated the effect of c-fos on c-jun- driven CPT promoter-chloramphenicol acyltransferase reporter gene expression in a HepG2 hepatoma cell cotransfection model. To investigate the possible role of cyclic adenosine monophosphate (cAMP) in the regulation of c-fos in vivo, we %%%treated%%%
either the sham-CLP group or the CLP group with either vehicle or cAMP. Results. Peritoneal sepsis in the rat model resulted in a four-fold increase in hepatic c-fos mRNA and c-fos protein. In the cotransfection model, c-fos significantly inhibited c-jun-induced chloramphenicol acyltransferase activity. %%%Treatment%%% with cAMP resulted in a 50% decrease in c-fos protein in either the sham-CLP or CLP group. Conclusions. We conclude that (1) sepsis increases hepatic c-fos transcription and translation, (2) c-fos inhibits c-jun-induced CPT gene expression, and (3) cAMP probably does not directly mediate the increase in c-fos after sepsis.

19/3,AB/70 (Item 16 from file: 73)

DIALOG(R)File 73:EMBASE

05032789 EMBASE No: 1992173005
Testing and characterizing enzymes and membrane-bound carrier proteins acting on amphipathic ligands in the presence of bilayer membrane material and soluble binding protein. Application to the uptake of oleate into isolated cells
Heirwegh K.P.M.; Meuwissen J.A.T.P.
Laboratory of Hepatology, Faculty of Medicine, Katholieke Universiteit Leuven,Gasthuisberg, 3000-Leuven Belgium
Biochemical Journal (BIOCHEM. J.) (United Kingdom) 1992, 284/2 (353-361)
CODEN: BIJOA ISSN: 0264-6021
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

1. A multiphasic modelling approach (Heirwegh, Meuwissen, Vermeir and De
Smedt (1988) Biochem. J. 254, 101-108) is applied to systems containing poorly water-soluble amphipathic reactants, membrane material, soluble binding protein and acceptor protein (enzyme or membrane-bound carrier protein). 2. The field of application is constrained by the assumptions (i) that the amount of acceptor-bound substrate is small compared with the total amount and (ii) that all preceding chemical reactions and steps of mass transport are rapid compared with the chemical change monitored. 3. Initial-rate formulae for systems in which an acceptor interacts with unbound or protein-bound ligand are given. The saturation curves are near-hyperbolic or sigmoidal, depending both (i) on the form of ligand (unbound or protein-bound) acted upon by the acceptor and (ii) on whether the assays are performed at constant concentration of soluble
%%%binding%%%
%%%protein%%% %%%C%%%(p) or at constant substrate/binding-site molar ratio
R(s). 4. Several %%%diagnostic%%% features permit unequivocal distinction
between acceptor action on unbound or protein-bound substrate. In the former case, saturation curves, run at the same constant concentration of one of several binding proteins of increasing binding affinity, will show progressively increasing inhibition, the shape changing from near-hyperbolic at K(m)' < Kinf 1' to sigmoidal at K(m)' > Kinf 1'. K(m)' is the effective Michaelis constant of the acceptor and Kinf 1' the effective dissociation constant of the binding sites of the soluble protein (for the sites with the higher binding affinity, if several classes of binding site are present on the protein). Alternatively, the maximum velocity obtained at constant R(s) <= 1 should increase hyperbolically with R(s)/(1-R(s)) for a binding protein with a single class of binding site. The formula that applies when the binding protein contains two classes of independent binding site is also available. When the acceptor acts on protein-bound ligand, the maximum velocity obtained at constant binding-protein concentration, C(p), increases hyperbolically with C(p). 5. Application of these and additional criteria to initial-rate data on the uptake of oleate into isolated cells supports a mechanism of carrier-mediated uptake of the unbound ligand and allows one to clarify some observations that hitherto had been poorly explained. 6. The influence of soluble binding protein on the reaction and substrate specificities of ligand/acceptor interaction is also discussed. 7. In its present state, data %%%treatment%%% for 'double binding-protein systems' generally requires separate determination of the binding parameters of the soluble binding protein. Possible designs for direct application of data-fitting procedures are briefly discussed. 8. Details about the units used and about the derivation of ligand distribution functions, kinetic formulae and their properties, and formulae for interconversion of parameter values to various concentration scales have been deposited as Supplementary Publication SUP 50169 (16 pages) at the British Library Document Supply Centre, Boston Spa,
Wetherby, West Yorkshire LS23 7BQ, U.K., from whom copies can be obtained
on the terms indicated in Biochem. J. (1992) 281, 5.

19/3,AB/71 (Item 17 from file: 73)
DIALOG(R)File 73:EMBASE

04928181 EMBASE No: 1992068397
A phosphorylation site located in the NHinf 2-terminal domain of c-Myc increases transactivation of gene expression
Seth A.; Alvarez E.; Gupta S.; Davis R.J.
Howard Hughes Medical Inst., Program in Molecular Medicine, Univ. of MA
Medical School, 373 Plantation St.,Worcester, MA 01605 United States
Journal of Biological Chemistry (J. BIOL. CHEM.) (United States) 1991 , 266/35 (23521-23524)
CODEN: JBCHA ISSN: 0021-9258
DOCUMENT TYPE: Journal; Article
LANGUAGE: ENGLISH SUMMARY LANGUAGE: ENGLISH

The c-myc gene encodes a sequence-specific DNA-%%%binding%%% %%%protein%%% (%%%c%%%-Myc) that forms leucine zipper complexes and can act
as a transcription factor. Growth factor stimulation of cells causes the phosphorylation of the c-Myc transcriptional activation domain at Sersup 6sup 2 within a proline-rich region that is highly conserved among members of the Myc family (Alvarez, E., Northwood, I.C., Gonzalez, F. A., Latour, D. A., Seth, A., Abate, C., Curran, T., and Davis, R.J. (1991) J. Biol. Chem. 266, 15277-15285). This phosphorylation site is a substrate for growth factor-regulated MAP kinases and for the cell cycle-dependent protein kinase p34(cdc2). We report that serum %%%treatment%%% of cells results in a marked increase in the transactivation of gene expression mediated by the c-Myc transcriptional activation domain. A point mutation at the site of growth factor-stimulated phosphorylation (Sersup 6sup 2) decreases the serum induction of transactivation. These data indicate that the c-Myc transcriptional activation domain may be a direct target of signal transduction pathways.

19/3,AB/72 (Item 1 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08935719 97058628
Effects of perturbations of the hypothalamic-pituitary-adrenal axis on the acute phase response: altered C/EBP and acute phase response gene expression in lipopolysaccharide-%%%treated%%% rats.
Eastman HB; Fawcett TW; Udelsman R; Holbrook NJ
Gene Expression and Aging Section, National institute on Aging, Baltimore, Maryland 21224, USA.
Shock (UNITED STATES) Oct %%%1996%%%, 6 (4) p286-92, ISSN 1073-2322
Journal Code: CAE
Languages: ENGLISH
Document type: JOURNAL ARTICLE
In this study, we investigated the influence of long term perturbations of the hypothalamicpituitary-adrenal axis on the acute phase response elicited following lipopolysaccharide (LPS) challenge in rats. Specifically, we examined the effects of either long term absence of glucocorticoids (adrenalectomized rats %%%treated%%% with placebo chronic
release pellets) or extended exposure to pharmacologic levels of glucocorticoids (adrenalectomized rats %%%treated%%% with dexamethasone
chronic release pellets) on the expression of selected acute phase proteins and various members of the CCAAT/enhancer-%%%binding%%% %%%protein%%% (
%%%C%%% /EBP) family of transcription factors. Both hypothalamic-pituitary-adrenal axis manipulations resulted in a reduction of the acute phase response as assessed by the LPS-mediated induction of acute phase proteins and C/EBP gene expression, with dexamethasone %%%treatment%%% exhibiting a greater inhibitory effect than adrenalectomy.
Induction of hemopexin, alpha 1-acid glycoprotein, alpha 2-macroglobulin, GADD153, C/EBP beta, and C/EBP delta mRNAs by LPS were all abolished in
dexamethasone-%%%treated%%% rats. These findings have direct implications
for patients undergoing chronic high dose glucocorticoid therapy.

19/3,AB/73 (Item 2 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

08781649 96362667
Modulation of myosin filament organization by C-protein family members.
Seiler SH; Fischman DA; Leinwand LA

Department of Microbiology and Immunology, Albert Einstein College of Medicine, Bronx, New York, USA.
Molecular biology of the cell (UNITED STATES) Jan %%%1996%%%, 7 (1)
p113-27, ISSN 1059-1524 Journal Code: BAU
Contract/Grant No.: 5T32-HL07675, HL, NHLBI; AR-32147, AR, NIAMS;
GM-29090, GM, NIGMS
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We have analyzed the interactions between two types of sarcomeric proteins: myosin heavy chain (MyHC) and members of an abundant thick filament-associated protein family (myosin-binding protein; MyBP). Previous work has demonstrated that when MyHC is transiently transfected into mammalian nonmuscle COS cells, the expressed protein forms spindle-shaped
structures consisting of bundles of myosin thick filaments. Co-expression of MyHC and MyBP-C or -H modulates the MyHC structures, resulting in
dramatically longer cables consisting of myosin and MyBP encircling the nucleus. Immunoelectron microscopy indicates that these cable structures are more uniform in diameter than the spindle structures consisting solely of MyHC, and that the myosin filaments are compacted in the presence of MyBP. Deletion analysis of MyBP-H indicates that cable formation is dependent on the carboxy terminal 24 amino acids. Neither the MyHC spindles
nor the MyHC/MyBP cables associate with the endogenous actin cytoskeleton
of the COS cell. While there is no apparent co-localization between these structures and the microtubule network, colchicine %%%treatment%%% of the
cells promotes the formation of longer assemblages, suggesting that cytoskeletal architecture may physically impede or regulate polymer formation/extension. The data presented here contribute to a greater understanding of the interactions between the MyBP family and MyHC, and
provide additional evidence for functional homology between MyBP-C and
MyBP-H.

19/3,AB/74 (Item 3 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

08764339 96336108
Growth hormone-binding protein related immunoreactivity is regulated by the degree of insulinopenia in diabetes mellitus.
Kratzsch J; Keliner K; Zilkens T; Schmidt-Gayk H; Selisko T; Scholz GH
Department of Clinical Chemistry, University of Leipzig, Germany.
Clinical endocrinology (ENGLAND) Jun %%%1996%%%, 44 (6) p673-8, ISSN
0300-0664 Journal Code: DCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
OBJECTIVE: Derangements in the GH/IGF axis are common in patients with
diabetes mellitus. In insulin-dependent diabetes mellitus (IDDM), these disturbances seem to be due to a partial defect in GH action on its own receptor or via a post-receptor defect. In non-insulin-dependent diabetes mellitus (NIDDM), data are limited, and the regulation of the GH receptor (GHR) remains unclear. However, animal studies with diabetic rats demonstrated that the GHR density may be influenced by insulin disposal at the hepatocyte. With respect to this hypothesis we studied the relation between peripheral insulin status and the serum GH-binding protein (GHBP), which reflects indirectly the GHR density in the tissues. Patients with IDDM were compared to a NIDDM group as well as to a group of healthy
subjects. DESIGN AND PATIENTS: Basal blood samples for the determination of
serum GHBP, GH, and IGF-I were obtained from patients with IDDM (n = 27),
subjects with NIDDM (n = 112) and healthy controle (n = 42). Insulin, proinsulin, C-peptide and IGF-binding protein 1 (IGFBP-1) serum levels were used to estimate the insulin status in diabetic patients. RESULTS: GHBP serum levels were significantly lower in patients with IDDM than in either NIDDM or controls ($P < 0.001$). Conversely, the IGF-I levels were reduced in
both groups of diabetics. A subgroup of hypoinsulinaemic NIDDM patients showed significantly decreased GHBP concentrations ($P < 0.05$) compared to
the NIDDM sub-group with hyperinsulinaemia. Furthermore, GHBP levels were
significantly decreased in insulin-%%%treated%%% patients with NIDDM
compared to either non-insulin-requiring subjects or normal controls ($P < 0.05$). A significant direct relation was found between levels of GHBP and total insulin dose ($P < 0.01$) in patients with IDDM. In the NIDDM group, GHBP was correlated with proinsulin ($P < 0.001$), C-peptide ($P < 0.01$), Insulin ($P < 0.05$) and inversely with IGFBP-1 ($P < 0.001$). Multiple linear regression analysis indicated a significant contribution of proinsulin and IGFBP-1 to the variation of GHBP. CONCLUSIONS: Decreased GHBP levels in
IDDM as well as in NIDDM correlate with insulinopenia. Since the degree of
insulinopenia depends on the capability of the beta-cells to secrete proinsulin, C-peptide and insulin, we hypothesize that these hormones at least partially influence the serum level of GHBP. Low GHBP levels may reflect a reduced GH receptor density and a concomitant GH insensitivity, which leads to an impaired IGF generation in insulin-deficient patients.

19/3,AB/75 (Item 4 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

08499010 96162443
The protein tyrosine kinase Fyn activates transcription from the HIV promoter via activation of NF kappa B-like DNA-binding proteins.
Hohashi N; Hayashi T; Fusaki N; Takeuchi M; Higurashi M; Okamoto T; Semba
K; Yamamoto T
Department of Oncology, University of Tokyo, Japan.
International immunology (ENGLAND) Nov %%%1995%%%, 7 (11) p1851-9,
ISSN 0953-8178 Journal Code: AY5
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Protein tyrosine kinase p59fyn (Fyn) associates with the TCR-CD3 complex,
which suggests that Fyn plays a significant role in the signal transduction involving TCR complex. In addition to cellular genes, viral promoters such as the HIV long terminal repeat (LTR) are also activated upon T cell activation. To elucidate the functional significance of Fyn in the expression of viral promoters, we transfected a Fyn-expression vector together with a reporter plasmid containing the chloramphenicol acetyltransferase gene driven by HIV LTR into a human T cell line, Jurkat. In this assay, Fyn stimulated the promoter in HIV LTR when the transfected cells were %%%treated%%% with both concanavalin A and PMA as an
antigen-mimic stimulation. This activation required the intact SH2 domain of Fyn. Mutational analysis of HIV LTR showed that the NF kappa B binding
sites were responsible for this effect. Electrophoretic mobility shift assays and UV cross-linking experiments showed that activation of T cells by anti-CD3 antibody induced four kappa B-binding proteins (50, 60, 65 and 100 kDa) in Fyn-overexpressing cells more efficiently than in the parental cells. Our results suggested that Fyn was able to regulate expression of a subset of genes via kappa B-binding proteins upon T cell activation.

19/3,AB/76 (Item 5 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

07974835 94327567
Induction of GADD153, a CCAAT/enhancer-%%%binding%%% %%%protein%%% (
%%%C%%% /EBP)-related gene, during the acute phase response in rats.
Evidence for the involvement of C/EBPs in regulating its expression [published erratum appears in J Biol Chem 1995 Jun 16;270(24):14842]
Sylvester SL; ap Rhys CM; Luethy-Martindale JD; Holbrook NJ
Section on Gene Expression and Aging, National Institute on Aging, Baltimore, Maryland 21224.
Journal of biological chemistry (UNITED STATES) Aug 5

%%%1994%%%, 269
(31) p20119-25, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
CCAAT/enhancer-binding proteins (C/EBPs) comprise a homologous group of
transcriptional regulators that control liver and fat differentiation and are involved in regulating the expression of acute phase reactants during the host response to inflammation. GADD153, a unique member of the C/EBP
family, has been proposed to act as a dominant negative inhibitor of other C/EBPs, but little is known about its expression in liver or its role in the processes described above. We have examined its expression during the acute phase response (APR) and have shown that like C/EBP beta and C/EBP
delta, GADD153 mRNA is markedly induced in livers of rats %%%treated%%%
with lipopolysaccharide to initiate the APR. Interestingly, its induction is temporally delayed relative to that of C/EBP beta and C/EBP delta but is similar to that of acute phase reactants shown to be regulated by C/EBPs. Footprint analysis of the GADD153 promoter showed binding of proteins in liver extracts of both untreated and lipopolysaccharide-injected rats to a putative C/EBP regulatory site. Gel shift analysis showed that although present constitutively, binding activity was increased in extracts from lipopolysaccharide-%%%treated%%% animals. Both C/EBP alpha and C/EBP beta
were shown to contribute to the binding activity with the contribution by C/EBP beta increasing during the APR. Support for the functional role of this C/EBP-binding site and its interaction with C/EBPs in regulating GADD153 expression was obtained with cultured HepG2 hepatoma cells in which
overexpression of C/EBP beta was found to transactivate expression of a plasmid containing the GADD153 promoter linked to a reporter gene. These
findings suggest that the GADD153 gene is itself regulated by C/EBPs during the host response to inflammation and that GADD153 is likely to contribute to the regulation of other genes whose expression is altered during the APR.

19/3,AB/77 (Item 6 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

07708175 94109099
Insulin therapy increases low plasma growth hormone binding protein in children with new-onset type 1 diabetes.
Arslanian SA; Menon RK; Gierl AP; Heil BV; Foley TP Jr
Division of Pediatric Endocrinology, Metabolism and Diabetes Mellitus, Children's Hospital, University of Pittsburgh, PA.
Diabetic medicine (ENGLAND) Nov %%%1993%%%, 10 (9) p833-8, ISSN
0742-3071 Journal Code: DME
Contract/Grant No.: 5 MO1-RR00086-25 (GC RC), RR, NCRR; R29 HD27503-02,
HD, NICHD
Languages: ENGLISH
Document type: JOURNAL ARTICLE
This study was undertaken (1) to evaluate growth hormone binding protein (GHBP) levels in newly %%%diagnosed%%% patients with Type 1 diabetes before
and after insulin therapy and (2) to determine the relationship of GHBP to glycaemic control, C-peptide level and blood pH. GHBP, expressed as a percentage of (125I)GH bound, was determined in 33 patients with Type 1 diabetes (M/F = 19/14, 12.3 +/- 0.4 years) before (day 0), after 5 days (day 5) and after 3 months (month 3) of insulin therapy. At day 0, GHBP was lower in Type 1 diabetes compared with 38 matched healthy control subjects (3.9 +/- 0.4 vs 8.2 +/- 0.4%, $p < 0.001$). There was no significant improvement in GHBP at day 5 (4.4 +/- 0.3%). At month 3, GHBP increased to
(6.0 +/- 0.4%, $p < 0.001$ vs day 0), but was still lower than controls, $p < 0.001$. At day 0 GHBP correlated with BMI ($r = 0.50$, $p = 0.001$), blood glucose ($r = -0.43$ $p = 0.006$) and pH ($r = 0.48$, $p = 0.004$), but not HbA1. GHBP at month 3 correlated with day 0 C-peptide ($r = 0.41$, $p = 0.02$). Thus, (1) circulating GHBP is low in newly %%%diagnosed%%% patients with Type 1
diabetes, and increases after 3 months of insulin therapy but does not normalize and (2) the severity of biochemical derangement and residual beta-cell function at %%%diagnosis%%% may determine GHBP status and its
recovery. We conclude that insulin is an important modulator of GH binding protein in newly %%%diagnosed%%% children with Type 1 diabetes.

19/3,AB/78 (Item 7 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

07375498 92084631
A phosphorylation site located in the NH2-terminal domain of c-Myc increases transactivation of gene expression.
Seth A; Alvarez E; Gupta S; Davis RJ
Program in Molecular Medicine, University of Massachusetts Medical School, Worcester 01605.
Journal of biological chemistry (UNITED STATES) Dec 15 %%%1991%%%, 266
(35) p23521-4, ISSN 0021-9258 Journal Code: HIV
Contract/Grant No.: GM37845, GM, NIGMS; CA39240, CA, NCI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The c-myc gene encodes a sequence-specific DNA-%%%binding%%%
%%%protein%%% (%%%c%%%-Myc) that forms leucine zipper complexes and can act
as a transcription factor. Growth factor stimulation of cells causes the phosphorylation of the c-Myc transcriptional activation domain at Ser62 within a proline-rich region that is highly conserved among members of the Myc family (Alvarez, E., Northwood, I.C., Gonzalez, F. A., Latour, D. A., Seth, A., Abate, C., Curran, T., and Davis, R. J. (1991) J. Biol. Chem. 266, 15277-15285). This phosphorylation site is a substrate for growth factor-regulated MAP kinases and for the cell cycle-dependent protein kinase p34cdc2. We report that serum %%%treatment%%% of cells results in a
marked increase in the transactivation of gene expression mediated by the c-Myc transcriptional activation domain. A point mutation at the site of growth factor-stimulated phosphorylation (Ser62) decreases the serum induction of transactivation. These data indicate that the c-Myc transcriptional activation domain may be a direct target of signal transduction pathways.

19/3,AB/79 (Item 8 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
(c) format only 2000 Dialog Corporation. All rts. reserv.

07134005 93015930
Calcium ionophore A23187 induces expression of the growth arrest and DNA
damage inducible CCAAT/enhancer-%%%binding%%%
%%%protein%%% (%%%C%%%
/EBP)-related gene, gadd153. Ca2+ increases transcriptional activity and mRNA stability.
Bartlett JD; Luethy JD; Carlson SG; Sollott SJ; Holbrook NJ
Laboratory of Molecular Genetics, National Institute on Aging, Baltimore, Maryland 21224.
Journal of biological chemistry (UNITED STATES) Oct 5 %%%1992%%%, 267
(28) p20465-70, ISSN 0021-9258 Journal Code: HIV
Languages: ENGLISH
Document type: JOURNAL ARTICLE
gadd153 is a CCAAT/enhancer-%%%binding%%%
%%%protein%%% (%%%C%%%
/EBP)-related gene whose expression is induced in response to growth arrest and DNA damage. This investigation explored the possibility that Ca2+ might play a role in regulating expression of gadd 153. We have demonstrated that %%%treatment%%% of HeLa cells with the calcium ionophores A23187 and
ionomycin leads to the induction of gadd153 mRNA. The induction was rapid;
increases in mRNA were detected by 90 min of %%%treatment%%%, and near
maximum levels were achieved within 5-h exposure to A23187. Elevated mRNA
levels resulted from both an increase in the rate of gadd153 transcription and an increase in the stability of the gadd153 mRNA. The response was not dependent on protein kinase C nor was it coupled to c-fos expression.

Buffering intracellular and extracellular Ca2+ by combined %%%treatment%%% with BAPTA-AM (acetoxymethyl ester form of bis(aminophenoxy)ethane N,N'-tetraacetic acid) and EGTA prevented the induction of gadd153 mRNA by A23187. In addition, these %%%treatments%%% prevented the induction of gadd153 mRNA in response to the DNA damaging agent methyl methanesulfonate. We conclude that intracellular Ca2+ plays a role in regulating gadd153 expression. More specifically, Ca2+ likely plays a role in the induction of gadd153 mRNA following DNA damage.

19/3,AB/80 (Item 9 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06976371 92041747
Synthesis of protein C in human umbilical vein endothelial cells.
Tanabe S; Sugo T; Matsuda M
Institute of Hematology, Jichi Medical School, Tochigi.
Journal of biochemistry (JAPAN) Jun %%%1991%%%, 109 (6) p924-8, ISSN 0021-924X Journal Code: HIF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
By monitoring the activation of protein C and the regulation of factor Xa-catalyzed thrombin formation by the activated protein C (APC) on the surface of human umbilical vein endothelial cells (HUVEC), we found that functional protein C was synthesized in cultured HUVEC and expressed thereon in the presence of vitamin K. Furthermore, without exogenously added protein S, time-dependent and saturable accumulation of APC (20 fmol APC/10(5) cells) on the surface of HUVEC was observed. During prothrombin activation by the complex of membrane-bound factor Xa and endogenous factor Va formed on the surface of HUVEC, APC was generated, and the rate of thrombin formation decreased. %%%Treatment%%% of HUVEC with an antibody that inhibits the APC-catalyzed inactivation of endogenous factor Va clearly quenched the activity of surface-associated APC. Immunostaining of HUVEC with a horseradish peroxidase (HRP)-conjugated antibody that solely recognizes human protein C confirmed the presence of protein C on the surface of HUVEC. Northern blot analysis revealed that an about 1.8 kb mRNA species derived from HUVEC was hybridized with 32P-labeled protein C cDNA, as in the case of those from HepG2, which are known to synthesize normal protein C. The increase in the amount of protein C mRNA in HUVEC in parallel with cell growth provided supporting evidence for the synthesis of protein C during the culture of HUVEC. These results indicate that blood coagulation is regulated by endogenously generated and activated protein C, together with or without protein S, through inactivation of factor Va on the surface of endothelial cells.

19/3,AB/81 (Item 10 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06919643 91266936
Different glycoforms of human thrombomodulin. Their glycosaminoglycan-dependent modulatory effects on thrombin inactivation by heparin cofactor II and antithrombin III.
Koyama T; Parkinson JF; Sie P; Bang NU; Muller-Berghaus G; Preissner KT
Haemostasis Research Unit, Kerckhoff-Klinik, Bad Nauheim, Federal Republic of Germany.
European journal of biochemistry (GERMANY) Jun 15 %%%1991%%%, 198 (3) p563-70, ISSN 0014-2956 Journal Code: EMZ
Languages: ENGLISH
Document type: JOURNAL ARTICLE
The relationship between thrombomodulin-associated O-linked glycosaminoglycans (GAGs) and the exogenous GAGs heparin or dermatan sulfate was studied in the inhibition of thrombin by antithrombin III (AT III) or heparin cofactor II (HC II). Both rabbit thrombomodulin (TM) and two glycoforms (a high-Mr form containing GAGs and a low-Mr form lacking the majority of O-linked GAGs) of a recombinant human TM deletion mutant (rec-TM) were used. The rapid inactivation of thrombin by HC II in the presence of dermatan sulfate was prevented by both the high-Mr rec-TM and the rabbit TM. In contrast, both rabbit TM %%%treated%%% with chondroitin ABC lyase to remove O-linked GAGs and the low-Mr form of rec-TM had only weak protecting effects. In the absence of exogeneous dermatan sulfate, thrombin inhibition by a high concentration of HC II was slightly accelerated by the high-Mr form of rec-TM but protected by rabbit TM. When thrombin inhibition by AT III in the presence of heparin was studied, both high-Mr rec-TM and rabbit TM again invoked a similar reduction of inactivation rates, whereas in the absence of exogenous heparin, both high-Mr forms accelerated thrombin inhibition by AT III. The diverse reactivities of various forms of TM towards HC II and AT III were also observed during protein C activation by the thrombin-TM complex. These results suggest that thrombin activity at the vessel wall or in fluid phase may undergo major kinetic modulations depending on the type of protease inhibitor, the presence or absence of exogenous GAGs and the glycosylation phenotype of TM. The dependence of TM anticoagulant function on the presence of an intrinsic GAG moiety suggests that variant glycoforms of this endothelial cell cofactor may be expressed differently in a species-, organ-, or tissue-specific manner as a means to regulate TM function in diverse vasculatures.

19/3,AB/82 (Item 11 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

06058869 87296899
[Protein C, protein S]
Proteine C, proteine S.
Guillin MC; Bezeaud A
Annales de biologie clinique (FRANCE) %%%1987%%%, 45 (2) p184-90, ISSN 0003-3898 Journal Code: 4ZS
Languages: FRENCH Summary Languages: ENGLISH
Document type: JOURNAL ARTICLE ; English Abstract
Protein C is a potent inhibitor of blood coagulation, and, in addition, appears to be a profibrinolytic agent. In a first step, protein C must be converted to a serine protease. This activation is catalyzed by a complex formed between thrombin and thrombomodulin, an endothelial cell surface protein. Activated protein C exhibits its anticoagulant activity through the proteolytic inactivation of two blood coagulation cofactors, factors Va and VIIIa. This reaction requires phospholipids, originating from platelets or endothelial cells, and a cofactor protein, protein S. Protein S enhances the %%%binding%%% of activated %%%protein%%% %%%C%%% to phospholipids. In addition, activated protein C stimulates fibrinolysis, through the inactivation of the tissue plasminogen activator (tPA) inhibitor. An isolated constitutional, quantitative or qualitative, protein C or protein S deficiency increases the risk of thrombosis, the clinical features are different in the rare cases of homozygous protein C deficiency (neonatal purpura fulminans) or in the heterozygous patients (recurrent venous thrombosis in young adults). Acquired deficiency in protein C and S had been observed in liver disease, during vitamin K antagonists or L-Asparaginase %%%treatment%%% , and in disseminated intravascular coagulation.

19/3,AB/83 (Item 12 from file: 155)
DIALOG(R)File 155:MEDLINE(R)

05763963 89278077
Monoclonal antibodies to human thrombomodulin whose binding is

calcium
dependent.
Kimura S; Nagoya T; Aoki N
Tokyo Research Institute, Kowa Ltd.
Journal of biochemistry (JAPAN) Mar %%%1989%%%, 105 (3)
p478-83,
ISSN 0021-924X Journal Code: HIF
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Four monoclonal antibodies to human thrombomodulin were
characterized.
Binding of two of these antibodies was dependent on the presence of calcium ions, and approximately 5 mM calcium was required for their maximum binding. These two antibodies inhibited the binding of thrombin to thrombomodulin, thereby inhibiting activation of protein C catalyzed by thrombin-thrombomodulin complex. These two antibodies bind to a major active fragment formed by limited proteolytic digestions of thrombomodulin with elastase and trypsin, suggesting that the antibodies bind to the thrombin-binding site (or its vicinity) located in the epidermal growth factor (EGF)-homology domain. One of the other calcium-independent antibodies also inhibited the binding of thrombin and the activation of protein C, but the inhibition was very weak and was observed only when the antibody was present in a molar excess over thrombomodulin. This antibody did not bind to the protease digests of thrombomodulin. Another calcium-independent antibody did not inhibit either thrombin
%%%binding%%%
or %%%protein%%% %%%C%%% activation, but %%%bound%%% to the active
fragment of protease digests, suggesting that the antibody binds to a region other than the thrombin-binding site in the EGF-homology domain. These observations suggest that thrombomodulin undergoes a calcium-dependent conformational change which may occur in proximity to a
thrombin-binding site located in the EGF-homology domain.

19/3,AB/84 (Item 13 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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05599344 90028784
Discrimination of normal and abnormal prothrombin and protein C in plasma using a calcium ion-inhibited monoclonal antibody to a common epitope on several vitamin K-dependent proteins.
Church WR; Bhushan FH; Mann KG; Bovill EG
Department of Biochemistry, College of Medicine, University of Vermont, Burlington 05405.
Blood (UNITED STATES) Nov 15 %%%1989%%%, 74 (7)
p2418-25, ISSN
0006-4971 Journal Code: A8G
Contract/Grant No.: HL35058, HL, NHLBI; HL24804, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Vitamin K deficiency or administration of vitamin K antagonists results in the biosynthesis of abnormal des-gamma-carboxy forms of the vitamin K-dependent proteins. Monoclonal antibody H-11 binds several vitamin K-dependent proteins at a determinant that includes the first two residues of gamma-carboxyglutamic acid. Antibody H-11 binds fully carboxylated prothrombin and protein C in the presence of EDTA but binding is inhibited by the divalent metal ions, calcium, magnesium, and manganese. By contrast, des-gamma-carboxy prothrombin and %%%protein%%% %%%C%%% %%%bind%%% antibody
H-11 the same in the presence of EDTA or calcium ion. Antibody H-11 thus
appears to bind a conserved antigenic site containing gamma-carboxyglutamic acid that in the presence of divalent metal ion undergoes a conformational transition. This ability of antibody H-11 to bind des-gamma-carboxy prothrombin and protein C in the presence of calcium ion allowed the development of an immunoassay for these proteins in plasma. Prothrombin and
protein C from stably anticoagulated individuals receiving warfarin were characterized by their ability to bind antibody H-11 in the presence of calcium ion. Binding of prothrombin and protein C to antibody H-11 in the presence of calcium correlated temporally with warfarin administration. The inability of calcium ion to inhibit binding of antibody H-11 to abnormal prothrombin and protein C in plasma suggests that the circulating forms of both proteins following warfarin administration cannot undergo the metal ion-dependent conformational transition that includes sequence residues 1 through 12.

19/3,AB/85 (Item 14 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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05070140 87299786
Immunoaffinity purification of protein C by using conformation-specific monoclonal antibodies to protein C-calcium ion complex.
Nakamura S; Sakata Y
Biochimica et biophysica acta (NETHERLANDS) Aug 13 %%%1987%%%, 925 (2)
p85-93, ISSN 0006-3002 Journal Code: A0W
Languages: ENGLISH
Document type: JOURNAL ARTICLE
We isolated protein C from a barium citrate-adsorbed fresh plasma and human factor IX concentrate by immunoaffinity chromatography on a column of
Sepharose coupled with monoclonal antibodies to protein C. The antibodies used were conformation-specific monoclonal antibodies to the calcium-induced structure of protein C. %%%Protein%%% %%%C%%% was
%%%bound%%% to antibodies coupled with Sepharose in the presence of calcium
ions and was eluted with EDTA. This immunopurification resulted in a 13,000-fold purification of the fully functional zymogen from plasma. The immunoaffinity-isolated protein C was found to have higher amounts of single-chain protein C than conventionally isolated protein C when analyzed by sodium dodecyl sulfate-polyacrylamide gels under reduced conditions. The factor IX concentrate was applied to this Ca2+-dependent antibody JTC-3-immobilized Sepharose in the presence of 5 mM CaCl2, and protein C
with its gamma-carboxyglutamic acid (Gla) domain intact was firstly bound to this column and then eluted by metal chelation with EDTA. When flow-through fractions were applied again in the presence of Ca2+ to this column, modified protein C which had lost its N-terminal 42-residue peptide was weakly bound to this column. It was eluted in the absence of Ca2+. However, only a low percentage of modified protein C was detectable by an enzyme-linked immunosorbent assay using Ca2+-dependent monoclonal antibody
JTC-3 and peroxidase-labeled immunopurified polyclonal antibody. These results indicate that factor IX concentrate has both Gla-domain-intact and Gla-domainless protein C. Moreover, it suggests that Ca2+-dependent monoclonal antibody JTC-3 may recognize the coupled conformational change
of protein C induced by the combined effect of Ca2+ binding to the Gla domain and to other parts of protein C.

19/3,AB/86 (Item 15 from file: 155)
DIALOG(R)File 155:MEDLINE(R)
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04365921 84080815
Determination of functional levels of protein C, an antithrombotic protein, using thrombin-thrombomodulin complex.
Comp PC; Nixon RR; Esmon CT
Blood (UNITED STATES) Jan %%%1984%%%, 63 (1) p15-21, ISSN 0006-4971
Journal Code: A8G
Contract/Grant No.: 7 PO1 HL 30073-01, HL, NHLBI
Languages: ENGLISH
Document type: JOURNAL ARTICLE
Protein C is a vitamin K-dependent plasma protein. Activated protein C is a potent anticoagulant and enhances blood clot lysis. We have developed a functional assay for protein C in human plasma. The measurement of protein C is accomplished by the addition of thrombomodulin, an endothelial-cell-associated cofactor for protein C activation, and thrombin in a 1:1 molar complex. The activated protein C formed in the plasma is immunoadsorbed with goat anti-human protein C IgG-agarose. The immunoadsorbed activated protein C retains the ability to hydrolyze chromogenic substrates, and after unbound plasma proteins are removed by washing, the %%%bound%%% activated %%%protein%%% %%%C%%% is quantitated by
incubation with the substrate H-D-phe-pip-arg-p-nitroanilide (S-2238). Normal individuals have functional protein C levels of 3.9-5.9 micrograms/ml, with a mean value of 4.8 micrograms/ml. Individuals

undergoing warfarin anticoagulation and patients with advanced liver diseases have decreased levels, as do certain patients with evidence of intravascular clotting. Functional protein C levels correlate well with immunologic levels of the protein in the patient groups studied. Heparin enhances the rate of activated protein C inhibition, as monitored by recovery of activated protein C by immunoadsorption. A patient with recurrent venous thrombosis and abnormal functional protein C activity, but normal levels of antigen, has been identified.

19/3,AB/87 (Item 1 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0202115 DBA Accession No.: 96-12886 PATENT
DNA encoding human CCAAT/enhancer binding protein - antisense CCAAT/enhancer %%%binding%%% %%%protein%%% %%%C%%%/EBP-alpha gene
expression from vector for use in hepatoma, etc., gene therapy
AUTHOR: Darlington G J; Wilson D R; Wilde M
CORPORATE SOURCE: Houston, TX, USA.
PATENT ASSIGNEE: Baylor-Coll.Med. %%%1996%%%
PATENT NUMBER: US 5545563 PATENT DATE: 960813 WPI
ACCESSION NO.:
96-383675 (9638)
PRIORITY APPLIC. NO.: US 205506 APPLIC. DATE: 940304
NATIONAL APPLIC. NO.: US 205506 APPLIC. DATE: 940304
LANGUAGE: English
ABSTRACT: New DNA (I) encoding human CCAAT/enhancer %%%binding%%% %%%protein%%% %%%C%%%/EBP-alpha is claimed. The DNA sequence of (I) is disclosed. Also claimed are: a vector containing (I) for expression in a mammal cell, especially a hepatic cell; and nucleic acid complementary to (I), optionally labeled. The vector containing (I), preferably under the control of a tumor-specific promoter, can be used for gene therapy of cancer or other diseases. Also disclosed are: using the vector to inhibit hepatoma proliferation; a method for inducing proliferation of a hepatic cell, which involves administering a vector expressing an antagonist of C/EBP-alpha (especially antisense C/EBP-alpha); a method for %%%diagnosis%%% of hepatoma using the antisense sequence; a method for determining the carcinogenic potential of a chemical using a transgenic mouse with mutant C/EBP-alpha; and the transgenic mouse. In an example, C/EBP-alpha gene was isolated from a phage lambda-gt10 gene bank of genomic DNA from Hep3B2 cells. The gene bank was probed with a rat C/EBP-alpha sequence and a clone containing the whole human C/EBP-alpha gene and 2.2 kb of 5' flanking sequence was isolated. (23pp)

19/3,AB/88 (Item 2 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0192541 DBA Accession No.: 96-02734 PATENT
Calcium-binding monoclonal antibody immunoreactive with protein-C - production by antibody engineering, for application as an antitumor, and in immunoassay
AUTHOR: Rezaie A; Esmon C T
CORPORATE SOURCE: Oklahoma City, OK, USA.
PATENT ASSIGNEE: Oklahoma-Med.Res.Found. %%%1995%%%
PATENT NUMBER: WO 9534652 PATENT DATE: 951221 WPI
ACCESSION NO.:
96-049681 (9605)
PRIORITY APPLIC. NO.: US 259321 APPLIC. DATE: 940610
NATIONAL APPLIC. NO.: WO 95US7372 APPLIC. DATE: 950609
LANGUAGE: English
ABSTRACT: A recombinant calcium-dependent monoclonal antibody (MAb) is immunoreactive with an epitope in the activation peptide region of the heavy chain of protein-C (EC-3.4.21.69) defined by EDQVDPRLIDGK in combination with calcium, and inhibits protein-C activation by thrombin-thrombomodulin. Preferably, the MAb is composed of amino acids 20-129 or 23-129 of a 129 amino acid specified protein sequence. The MAb is encoded in part by a 417 bp specified DNA sequence, or bases 58-417 of this, or a 387 bp DNA sequences or bases 67-387 of this. The MAb is further composed of a carrier, and optionally a cytokine or a cytokine-inhibitor to coagulate microvasculature in tumors but not in the absence of the MAb. The MAb may be bound to a detectable label, or it may be immobilized on a substrate. The MAb us useful in the %%%treatment%%% of tumor patients. The immobilized MAb can be used to purify protein-C from a biological fluid and in %%%diagnostic%%% assays. The MAb contains a DNA sequence from the hypervariable region of the HPC-4 antibody, and is useful in mimicking HPC-4 %%%protein%%%-%%%C%%% %%%binding%%%. (41pp)

19/3,AB/89 (Item 3 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0189946 DBA Accession No.: 96-00717 PATENT
DNA encoding granulocyte-colony stimulating factor binding region - recombinant granulocyte-colony stimulating factor receptor binding region-maltose binding protein fusion protein production by vector expression in Escherichia coli
CORPORATE SOURCE: Japan.
PATENT ASSIGNEE: Tanpaku-Eng.Res.Inst. %%%1995%%%
PATENT NUMBER: JP 7227288 PATENT DATE: 950829 WPI
ACCESSION NO.:
95-331525 (9543)
PRIORITY APPLIC. NO.: JP 93321862 APPLIC. DATE: 931221
NATIONAL APPLIC. NO.: JP 94116252 APPLIC. DATE: 940530
LANGUAGE: JA
ABSTRACT: A DNA encoding a protein derived from the ligand-binding region of a granulocyte-colony stimulating factor receptor is claimed. Also claimed are: (a) a recombinant plasmid containing the DNA under the control of an Escherichia coli gene expression system; (b) a recombinant plasmid capable of expressing a fusion protein consisting of the protein and an E. coli maltose %%%binding%%% %%%protein%%%; (%%%c%%%) E. coli transformed with the recombinant plasmids; (d) a process for producing the protein involving culturing the transformed E. coli cells and recovering the recombinant product accumulated in the bacterium; and (e) protein produced by these recombinant methods. The protein may be used to elucidate the interaction between the granulocyte-colony stimulating factor receptor and its ligand, as well as to %%%treat%%% or prevent granulocyte-colony stimulating factor-dependent diseases (e.g. leukemia) or abnormalities such as abnormal growth of granulocytes. (21pp)

19/3,AB/90 (Item 4 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs

0102336 DBA Accession No.: 90-05027 PATENT
Human Protein-C derivative - chimeric gene cloning and expression, e.g. in CHO or BHK cell culture; DNA sequence
PATENT ASSIGNEE: Hoechst-Japan %%%1990%%%
PATENT NUMBER: EP 354504 PATENT DATE: 900214 WPI
ACCESSION NO.: 90-046218
(9007)
PRIORITY APPLIC. NO.: JP 88179144 APPLIC. DATE: 880809
NATIONAL APPLIC. NO.: EP 89114505 APPLIC. DATE: 890805
LANGUAGE: English
ABSTRACT: A derivative of human Protein-C is claimed, which has the N-terminal region with gamma-carboxylated Glu residues (Gla domain) replaced by the Gla domain of cattle Protein-C, or by a sequence with similar calcium-binding activity and/or enhanced Protein-C activity. A DNA sequence encoding the protein and a recombinant host cell (e.g. CHO or BHK cell culture) expressing the gene are also claimed. A DNA sequence encoding the human Gla domain (e.g. amino acid residues 1-43) is replaced with the DNA sequence encoding the Gla domain of cattle Protein-C. The prepro-sequence of human Protein-C may additionally be replaced with the prepro-sequence of cattle Protein-C, or with the prepro-sequence of menadione-dependent blood-clotting factors, such as

Factor-X. The hybrid proteins have an increased number of Glu residues (from 9 to 11). By the increased number of gamma-carboxylation sites, enhanced calcium-%%%binding%%% activity of %%%Protein%%%-%%%C%%% and improved activation of Protein-C is obtained. The activated Protein-C inhibits blood-clotting or accelerates fibrinolysis, and is used for %%%treating%%% blood-clotting disorders. (17pp)

19/3,AB/91 (Item 5 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0058193 DBA Accession No.: 87-02541 PATENT
Monoclonal antibody to human %%%protein%%% %%%C%%% %%%binding%%% a calcium ion at the Gla domain - construction of a hybridoma secreting monoclonal antibody; application to liver disease %%%diagnosis%%%
PATENT ASSIGNEE: Teijin %%%1986%%%
PATENT NUMBER: EP 205046 PATENT DATE: 861217 WPI ACCESSION NO.: 86-333583
(8651)
PRIORITY APPLIC. NO.: JP 85124388 APPLIC. DATE: 850610
NATIONAL APPLIC. NO.: EP 86107297 APPLIC. DATE: 860528
LANGUAGE: English
ABSTRACT: A new monoclonal antibody to human protein C does not recognize human %%%protein%%% %%%C%%% not %%%binding%%% a calcium ion at the Gla domain but recognizes human %%%protein%%% %%%C%%% which does %%%bind%%% a calcium ion at this position. The monoclonal antibody is used for determining or separating human protein C for detection of liver disease. Mice are immunized with human protein C and the spleen cells are extracted and fused with mouse myeloma cells. The resulting hybridoma cells are screened and selected cells isolated and used for the production of desired monoclonal antibody. The mice may be female BALB/c mice which may be immunized e.g. 3 times at 2 wk intervals i.p., then an injection is given i.v. prior to extraction of spleen cells. These are fused with e.g. P3-X63-Ag8-U1 myeloma cells using PEG 1,000 as the preferred fusogen. Hybridomas are cultured in e.g. HAT medium and screened by an ELISA. Hybridoma cells selected may be cloned by limiting dilution and injected into mice for production of ascites. The monoclonal antibodies obtained may be used for isolation of human %%%protein%%% %%%C%%% by %%%binding%%% to a carrier such as Sepharose.
(20pp)

19/3,AB/92 (Item 6 from file: 357)
DIALOG(R)File 357:Derwent Biotechnology Abs
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0036148 DBA Accession No.: 85-06937 PATENT
Membrane-bound polypeptide having antigenic determinants - useful for binding to herpes simplex virus
PATENT ASSIGNEE: Genentech %%%1985%%%
PATENT NUMBER: AU 8432424 PATENT DATE: 850307 WPI ACCESSION NO.:
85-099048 (8517)
PRIORITY APPLIC. NO.: US 587763 APPLIC. DATE: 840309
NATIONAL APPLIC. NO.: AU 8432424 APPLIC. DATE: 840827
LANGUAGE: English
ABSTRACT: A %%%diagnostic%%% product comprising membrane-bound polypeptide (I) having antigenic determinants capable of specific binding of complementary antibody is new. The (I) is functionally associated with a membrane of a recombinant stable continuous cell line capable of its production. A %%%diagnostic%%% kit is also described. Membrane-bound (I) are useful as %%%diagnostic%%% agents and are obtained in large amounts by recombinant DNA technology in non-pathogenic form. They may be obtained from a stable continuous cell line. As (I) are especially capable of binding herpes simplex virus specific antibodies, they may also be used in vaccines against the virus or to reduce the effects of an existing infection. The (I) is especially a glycoprotein (C or D) of herpes simplex virus type 1 or 2 and is capable of binding to the antibodies. It may be a fragment of %%%glycoprotein%%% %%%C%%% and then %%%binds%%% to types 1 or 2 or to type 1 alone. It may be linked to a label e.g. an enzyme, or to a solid surface. The %%%diagnostic%%% kit may contain unlabeled and labeled complementary antibody. (95pp)
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